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Docket Number	P-15822	Type a plus sign (+) inside this box -->	+

INVENTOR(s)/APPLICANT(s)

LAST NAME	FIRST NAME	MIDDLE NAME	RESIDENCE (CITY AND EITHER STATE OR FOREIGN COUNTRY)
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TITLE OF THE INVENTION (280 characters max)

BENZYL MORPHOLINE DERIVATIVES

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PATENT TRADEMARK OFFICE

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ENCLOSED APPLICATION PARTS (*check all that apply*)

X	Specification	Number of pages	74		Small Entity Statement
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METHOD OF PAYMENT (*check one*)

	A check or money order is enclosed to cover the Provisional filing fees	PROVISIONAL FILING FEE AMOUNT ($)	$160.00
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The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

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☐ Yes, the name of the U.S. Government agency and the Government contract number are:

Respectfully submitted,
SIGNATURE _____ Date 9/30/02

TYPED or PRINTED NAME PAUL J. GAYLO

REGISTRATION NO. (*if appropriate*) 36,808

☐ Additional inventors are being named on separately numbered sheets attached hereto

PROVISIONAL APPLICATION FOR PATENT FILING ONLY

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BENZYL MORPHOLINE DERIVATIVES

This invention relates to novel benzyl morpholine compounds, and to their use in inhibiting serotonin and norepinephrine reuptake.

Serotonin has been implicated in the aetiology of many disease states and has been found to be of importance in mental illnesses, depression, anxiety, schizophrenia, eating disorders, obsessive compulsive disorder (OCD) and migraine. Indeed many currently used treatments of these disorders are thought to act by modulating serotonergic tone. During the last decade, multiple serotonin receptor subtypes have been characterised. This has led to the realisation that many treatments act *via* the serotonergic system, such as selective serotonin reuptake inhibitor (SSRI) antidepressants which increase serotonin transmission, for example, the hydrochloride salt of fluoxetine.

Drugs that exert their main action on the norepinephrinergic system have been available for some time, however their lack of selectivity has made it difficult to determine specific clinical effects produced by a selective action on norepinephrine reuptake. Accumulating evidence indicates that the norepinephrinergic system modulates drive and energy, whereas the serotonergic system modulates mood. Thus norepinephrine appears to play an important role in the disturbances of vegetative function associated with affective, anxiety and cognitive disorders. Atomoxetine hydrochloride is a selective inhibitor of norepinephrine, and is currently under development for the treatment of attention deficit hyperactivity disorder (ADHD). Reboxetine is a marketed selective norepinephrine reuptake inhibitor for the treatment of depression.

Norepinephrine and serotonin receptors are known to interact anatomically and pharmacologically. Compounds that affect only serotonin have been shown to exhibit modulatory effects on norepinephrine, pointing toward an important relationship between the two neurotransmitter systems.

Duloxetine, (+)-*N*-methyl-3-(1-naphthalenyloxy)-2-thiophenepropanamine hydrochloride, inhibits the reuptake of both norepinephrine and serotonin, and is currently under development for the treatment of depression and urinary incontinence. The compound duloxetine was disclosed in US Patents 5,023,269 and 4,956,388.

According to the present invention there is provided a compound of formula (I)

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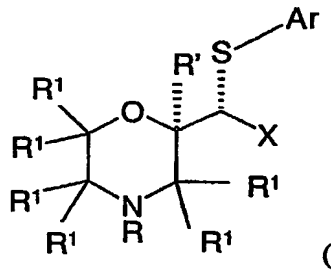


(I)

wherein

R is H;

Ar is an aromatic group selected from phenyl; X is a phenyl group; R' is H or C_1-C_4 alkyl; and each R_1 is independently H or C_1-C_4 alkyl; and pharmaceutically acceptable salts thereof.

The aromatic group Ar may be substituted or unsubstituted phenyl. For example, Ar may be unsubstituted phenyl or, preferably, phenyl substituted with 1, 2, 3, 4 or 5 substitutents, preferably with 1 or 2, for example 1, substituent. The substituted phenyl group is preferably substituted in the 2-position. Suitable substitutents include C_1-C_4 alkyl, O(C_1-C_4 alkyl), S(C_1-C_4 alkyl), halo, and phenyl, optionally substituted with, for example, halo, C_1-C_4 alkyl or O(C_1-C_4 alkyl).

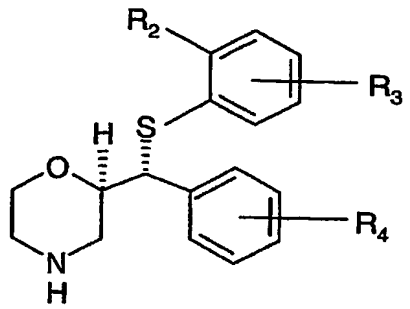
The group X may be substituted or unsubstituted phenyl. For example, X may be phenyl substituted with 1, 2, 3, 4 or 5 substituents, preferably with 1 substituent. Suitable substituents include C_1-C_4 alkyl, O(C_1-C_4 alkyl), and halo.

"C_1-C_4 alkyl" as used herein includes straight and branched chain alkyl groups of 1, 2, 3 or 4 carbon atoms, and may be unsubstituted or substituted. C_1-C_2 alkyl groups are preferred. Suitable substituents include halo. Thus the term "C_1-C_4 alkyl" includes haloalkyl.

"Halo" includes F, Cl, Br and I, and is preferably F or Cl.

Particularly preferred substituents for the Ar group include trifluoromethyl and methoxy.

A preferred group of compounds according to the present invention is represented by formula (II);



(II)

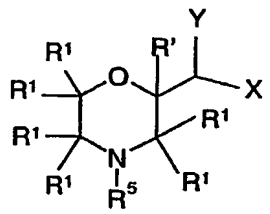
in which R_2 and R_3 are each independently selected from H, C_1-C_4 alkyl, O(C_1-C_4 alkyl), S(C_1-C_4 alkyl), halo, and phenyl; and

R_4 is selected from H, C_1-C_4 alkyl, and O(C_1-C_4 alkyl) and halo; and pharmaceutically acceptable salts thereof.

R_2 is preferably C_1-C_2 alkyl, O(C_1-C_2 alkyl), S(C_1-C_2 alkyl), Cl or F. R_3 is preferably H, Me or Cl. R_4 is preferably H, C_1-C_2 alkyl, O(C_1-C_2 alkyl), Cl or F.

The compounds of the present invention are dual reuptake inhibitors of serotonin and norepinephrine. Advantageously, they have a reduced interaction with the liver enzyme CYP2D6. They are particularly useful for the treatment of CNS disorders including depression, persistant pain and stress urinary incontinence.

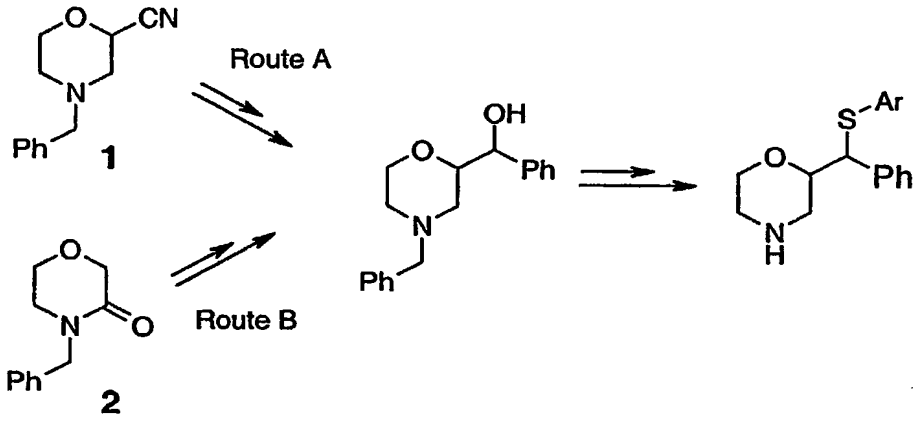
Compounds of the present invention may be prepared by reacting a compound of the formula II:



II

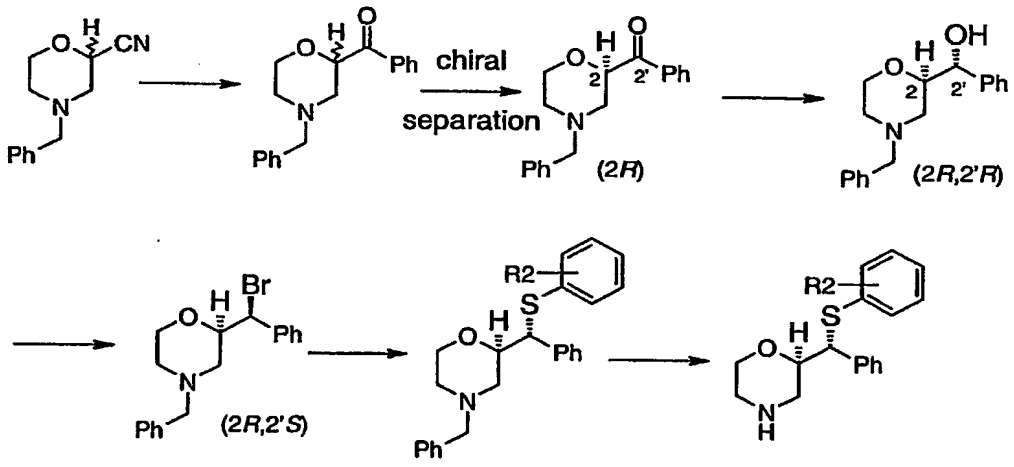
where R5 is a protecting group, e.g. benzyl, X, R' and R^1 are as formula I above and Y is a leaving group, with an aryl thiol. Examples of suitable leaving groups include halo and mesylate, but the nature of the leaving group is not critical.

Compounds of the present invention may be prepared by conventional organic chemistry techniques from N-benzyl-cyanomorpholine 1 (Route A) or N-benzyl-morpholinone 2 (Route B) as outlined in Scheme 1 below:



Scheme 1

More detail of Route A is given in Scheme 2:

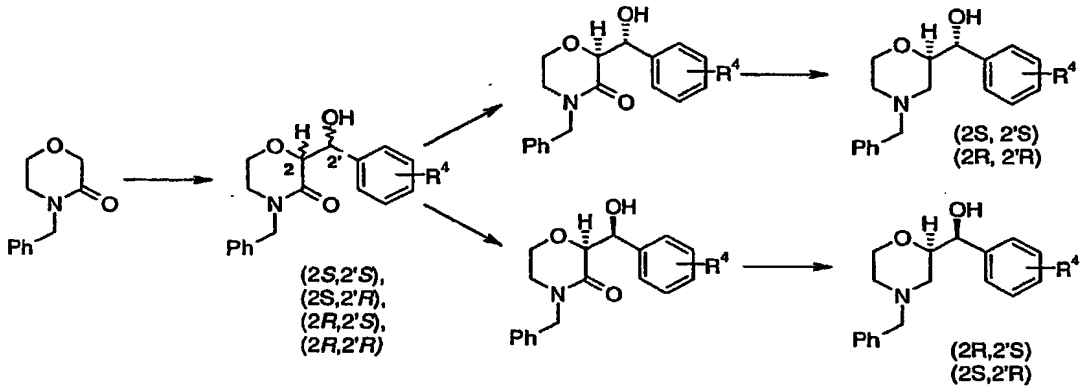


Scheme 2

The amino alcohol can be obtained by reaction of N-benzyl-cyanomorpholine with a Grignard reagent, followed by acid hydrolysis to give racemic phenyl ketone which may be separated on chiral HPLC. (2*R*)-Phenyl ketone may then be reduced with DIP-Cl to give the amino alcohol in high diastereomeric excess. The amino alcohol may be converted into the benzyl bromide to give the desired N-substituted aryl thio

morpholines after displacement with the requisite aryl thiol. Deprotection of the tertiary amine gives the final products.

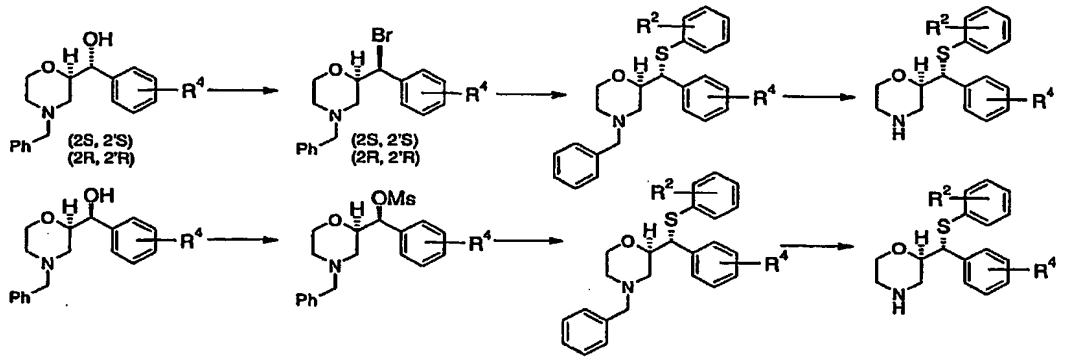
Detail of route B is given in Scheme 3:



Scheme 3

Treatment of *N*-benzyl morpholinone with a strong base such as lithium diisopropylamide at low temperature followed by addition of benzaldehyde gives aldol adducts as a 2:1 mixture of diastereomer pairs, which may be separated using conventional chromatographic techniques. Reduction with a borane reagent at elevated temperatures gives diasteremeric amino alcohol pairs.

Amino alcohol pair (2S,2'S) and (2R,2'R) may be converted to bromide and further to racemic aryl thio morpholines as outlined in Scheme 4. Amino alcohol pair (2R,2'S) and (2S,2'R) may be converted into the corresponding mesylate. Displacement with the requisite thiol, followed by removal of the nitrogen protecting group furnishes aryl thiol morpholines as racemic mixtures of two diastereomers. The racemic aryl thiol morpholines may be separated into enantiomerically pure products using chiral HPLC technology.



Scheme 4

Compounds of the present invention are selective inhibitors of the reuptake of both serotonin and norepinephrine and as such are useful as pharmaceuticals. They may be indicated in the treatment of disorders associated with serotonin and norepinephrine dysfunction in mammals, including depression, OCD, anxiety, memory loss, urinary incontinence, conduct disorders, ADHD, obesity, alcoholism, smoking cessation and pain. The compounds of the present invention are particularly suitable for the treatment of pain.

For clinical purposes, pain may be divided into two categories: acute pain and persistent pain. Acute pain is provoked by noxious stimulation produced by injury and/or disease of skin, deep somatic structures or viscera, or abnormal function of muscle or viscera that does not produce actual tissue damage. On the other hand, persistent pain can be defined as pain that persists beyond the usual course of an acute disease or a reasonable time for an injury to heal or that is associated with a chronic pathologic process that causes continuous pain or the pain recurs at intervals for months or years. If pain is still present after a cure should have been achieved, it is considered persistent pain. For the purpose of the present invention, persistent pain can be chronic non-remitting or recurrent. The difference in definition between acute and persistent pain is not merely semantic but has an important clinical relevance. For example, a simple fracture of the wrist usually remains painful for a week to 10 days. If the pain is still present beyond the typical course of treatment, it is likely that the patient is developing reflex sympathetic dystrophy, a persistent pain syndrome that requires immediate effective therapy. Early and effective intervention potentially prevents the undue disability and suffering, and avoids the potential development of a condition that becomes refractory to therapy.

Acute and chronic pain differ in etiology, mechanisms, pathophysiology, symptomatology, diagnosis, therapy, and physiological responses. In contrast to the transitory nature of acute pain, persistent pain is caused by chronic pathologic processes in somatic structures or viscera, by prolonged and sometimes permanent dysfunction of the peripheral or central nervous system, or both. Also, persistent pain can sometimes be attributed to psychologic mechanisms and/or environmental factors.

Current therapies for persistent pain include opiates, barbiturate-like drugs such as thiopental sodium and surgical procedures such as neurectomy, rhizotomy, cordotomy, and cordectomy.

References herein to pain are intended to refer to persistent pain.

The present invention provides pharmaceutical compositions comprising a compound of formula I or formula II or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier.

Further, the present invention provides a compound of formula I or a pharmaceutically acceptable salt thereof, for use as a pharmaceutical; and a compound of formula I or a pharmaceutically acceptable salt thereof, for use as a selective inhibitor of the reuptake of both serotonin and norepinephrine.

The present invention also provides the use of a compound of formula I or formula II, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for selectively inhibiting the reuptake of serotonin and norepinephrine; the use of a compound of formula I or formula II, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of disorders associated with serotonin and norepinephrine dysfunction in mammals; the use of a compound of formula I or formula II, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a disorder selected from depression, OCD, anxiety, memory loss, urinary incontinence, conduct disorders, ADHD, obesity, alcoholism, smoking cessation and pain; and the use of a compound of formula I or formula II, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a disorder selected from depression, stress urinary incontinence, and persistent pain. The present invention further provides a compound of formula I or formula II for treating disorders associated with serotonin and norepinephrine dysfunction in mammals, for example a disorder selected from depression, OCD, anxiety, memory

loss, urinary incontinence, conduct disorders, ADHD, obesity, alcoholism, smoking cessation and pain, especially depression, stress urinary incontinence, and persistent pain.

Further the present invention provides a method for selectively inhibiting the reuptake of serotonin and norepinephrine in mammals, comprising administering to a patient in need thereof an effective amount of a compound of formula I or formula II or a pharmaceutically acceptable salt thereof; a method for treating disorders associated with serotonin and norepinephrine dysfunction in mammals, comprising administering to a patient in need thereof an effective amount of a compound of formula I or formula II or a pharmaceutically acceptable salt thereof; and a method for treating a disorder selected from depression, OCD, anxiety, memory loss, urinary incontinence, conduct disorders, ADHD, obesity, alcoholism, smoking cessation and pain, especially depression, stress urinary incontinence or persistant pain, comprising administering to a patient in need thereof an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof.

The present invention includes the pharmaceutically acceptable salts of the compounds of formula I and formula II. Suitable salts include acid addition salts, including salts formed with inorganic acids, for example hydrochloric, hydrobromic, nitric, sulphuric or phosphoric acids, or with organic acids, such as organic carboxylic or organic sulphonic acids, for example, acetoxybenzoic, citric, glycolic, *o*- mandelic-l, mandelic-dl, mandelic d, maleic, mesotartaric monohydrate, hydroxymaleic, fumaric, lactobionic, malic, methanesulphonic, napsylic, naphthalenedisulfonic, naphtoic, oxalic, palmitic, phenylacetic, propionic, pyridyl hydroxy pyruvic, salicylic, stearic, succinic, sulfanilic, tartaric, 2-hydroxyethane sulphonic, toluene-p-sulphonic, and xinafoic acids.

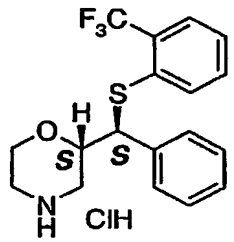
In addition to the pharmaceutically acceptable salts, other salts are included in the invention. They may serve as intermediates in the purification of compounds or in the preparation of other, for example pharmaceutically acceptable, acid addition salts, or are useful for identification, characterisation or purification.

It will be appreciated that compounds of formula I and formula II possess asymmetric carbon atoms, and that the present invention is directed specifically to individual stereoisomers. The particular stereochemistry of the present compounds is essential to the pharmacological profile of the compounds.

The following Examples illustrate compounds of the present invention and methods for their synthesis.

Stereochemical Conventions

The absolute stereochemistry of compounds according to the present invention may be determined by reference to X-ray crystallography for the following (2S,2'S) compound



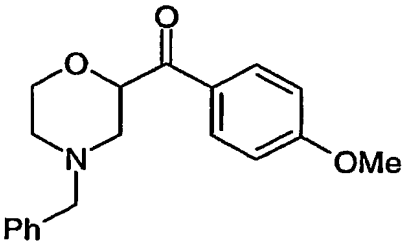
X-ray crystallographic data for the above compound is listed in Tables 1-6 herein.

All of the Examples herein were obtained as single isomers either through the use of chirally pure starting material or chiral separation methods, such as HPLC.

EXAMPLE 1

(2R)-2-((R)-[4-methoxyphenyl]{[2-methoxyphenyl]thio}methyl)morpholine hydrochloride

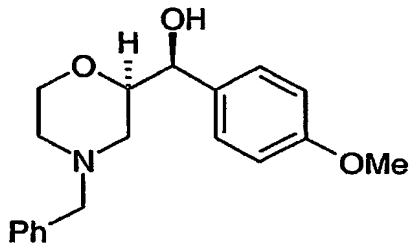
i) (+/-)-[4-Methoxyphenyl][(4-benzylmorpholin-2-yl]methanone



To stirred magnesium turnings (5.4g, 0.22mol) in dry THF (20ml) at room temperature under nitrogen was added sufficient 1,2-dibromoethane (ca. 0.3ml) to create an exotherm. A solution of 4-bromoanisole (13.90g, 74.25mmol) in dry THF (25ml) was

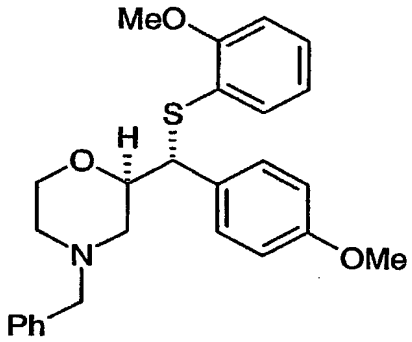
then added dropwise at a rate to maintain a gentle reflux. After addition, allowed to cool to below 30°C then added over 5 min. period to a stirred solution of 4-benzyl-2-cyanomorpholine (5.0g, 24.75mmol) in dry THF (50ml) cooled to –20°C under nitrogen. After addition stirred at room temperature for 30 min. then cooled to 0°C and added 5M HCl (25ml) dropwise. After 5 min. stirring, made basic by addition of 2M NaOH and the resulting suspension filtered through celite. The aqueous phase was separated and washed with diethyl ether (2x). The combined organic phases was dried over magnesium sulphate, filtered and evaporated to a yellow oil. The oil was purified by flash chromatography on silica eluting with ethyl acetate/heptane gradient 25/75 to 70/30 to give required product as a yellow oil (5.46g).

ii) (R)-[4-methoxyphenyl][(2S)-4-benzylmorpholin-2-yl]methanol and (S)-[4-methoxyphenyl][(2R)-4-benzylmorpholin-2-yl]methanol



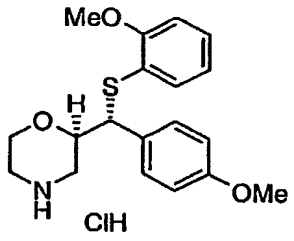
To a stirred solution of (+/-)-[4-Methoxyphenyl][4-benzylmorpholin-2-yl]methanone (5.40g, 17.36mmol) in methanol (60ml) at 5°C was added sodium borohydride (1.31g, 34.72mmol) portionwise. The mixture was stirred at room temperature for 1.5h, cooled to 10°C and added water to terminate reaction. Concentrated *in vacuo,* diluted with water and extracted with ethyl acetate (2x). Extracts washed with water and brine, dried over magnesium sulphate, filtered and evaporated to an oil. The crude mixture of diastereomers was purified and separated by flash chromatography on silica eluting with diethyl ether/toluene (3/2) to give the title diastereomer as a colourless oil (2.14g).

iii) (2R)-2-((R)-[4-methoxyphenyl]{[2-methoxyphenyl]thio}methyl)-4-benzylmorpholine and (2S)-2-((S)-[4-methoxyphenyl]{[2-methoxyphenyl]thio}methyl)-4-benzylmorpholine



A mixture of (R)-[4-methoxyphenyl][(2S)-4-benzylmorpholin-2-yl]methanol and (S)-[4-methoxyphenyl][(2R)-4-benzylmorpholin-2-yl]methanol (118mg, 0.376mmol), 2,2'-dimethoxydiphenyldisulphide (210mg, 0.75mmol) and tributylphosphine (152mg, 1.50mmol) in dry THF (2ml) was heated at reflux under nitrogen overnight. The reaction mixture was cooled to room temperature and evaporated to an oil. The crude oil was purified by flash chromatography on silica eluting with heptane/ethyl acetate (4/1 then 3/2) to give the product as a colourless oil (95mg).

iv) (2R)-2-((R)-[4-methoxyphenyl]{[2-methoxyphenyl]thio}methyl)morpholine hydrochloride



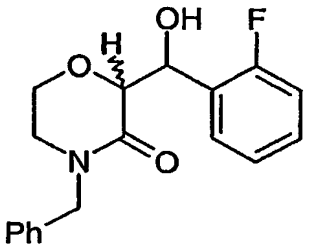
Stirred (2S)-2-((S)-[4-methoxyphenyl]{[2-methoxyphenyl]thio}methyl)-4-benzylmorpholine (2R)-2-((R)-[4-methoxyphenyl]{[2-methoxyphenyl]thio}methyl)-4-benzylmorpholine (618mg, 1.42mmol) with solid supported Hunig's base (2.40g, 8.52mmol) and α-chloroethyl chloroformate (2.0g, 14.21mmol) in dichloromethane (12ml) at room temperature under nitrogen for 4h. Filtered and concentrated *in vacuo* ,

dissolved oil in methanol and heated at 60°C for 1.5h. Cooled to room temperature and purified by SCX column chromatography eluting with ammonia/methanol (ca. 3M) gave a colourless oil. The desired diastereomer was separated on chiralcel-OJ column eluting with heptane/ethanol/dimethylethylamine (20/80/0.2) : 8.98 min. The required product was then obtained (60%de) after chiral chromatography on chiralpak-OD column eluting with heptane/isopropanol (70/30) : 17.41min. It was converted into the HCl salt, NMR (DMSO) 9.39 (2H, br. s), 7.3-7.1 (4H, m), 6.94-6.72 (4H, m), 4.6-4.5 (1H, m), 4.12-3.92 (2H, m), 3.85-3.62 (7H, m), 3.46-3.32 (1H, m), 3.20-3.08 (1H, m), 3.04-2.89 (2H, m). LCMS: *m/z* 346 $[M+H]^+$ @ Rt 4.24 min.

EXAMPLE 2:

(2*R*)-2-((*R*)-(2-Fluorophenyl){[2-methoxyphenyl]thio}methyl)morpholine hydrochloride

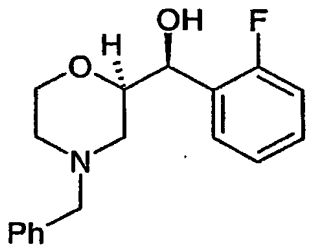
i) (2R)-2-[(R)-(2-fluorophenyl)(hydroxy)methyl]-4-benzylmorpholin-3-one, (2S)-2-[(S)-(2-fluorophenyl)(hydroxy)methyl]-4-benzylmorpholin-3-one, (2R)-2-[(S)-(2-fluorophenyl)(hydroxy)methyl]-4-benzylmorpholin-3-one and (2S)-2-[(R)-(2-fluorophenyl)(hydroxy)methyl]-4-benzylmorpholin-3-one



To a stirred solution of (+/-)-4-benzylmorpholin-3-one (10.0g, 0.052mol) and 2-fluorobenzaldehyde (7.74g, 0.062mol) in dry THF (80ml) cooled under nitrogen to –78°C was added dropwise a solution of lithium diisopropylamide in heptane/THF/ethylbenzene (2M, 31.2ml). After addition , stirred at –78°C for 0.5h then allowed to warm to 0°C before quenching with aqueous saturated ammonium chloride. Concentrated *in vacuo* and extracted with dichloromethane (2x). The extracts were dried over magnesium sulphate, filtered and evaporated to an oil. Purified on a pad of flash silica eluting with

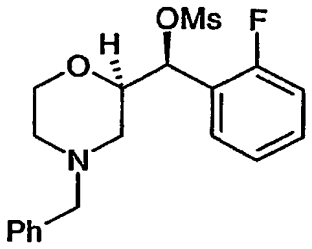
heptane/ethyl acetate (100/0, 80/20, 60/40 and 50/50) to give a 1:1 mixture of the diastereomers as a colourless oil (12.05g).

ii) (R)-[2-fluorophenyl][(2S)-4-benzylmorpholin-2-yl]methanol and (S)-[2-fluorophenyl][(2R)-4-benzylmorpholin-2-yl]methanol



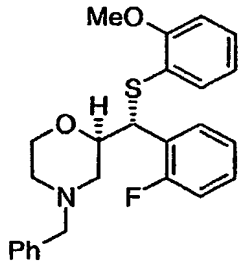
To a stirred solution of (2R)-2-[(R)-(2-fluorophenyl)(hydroxy)methyl]-4-benzylmorpholin-3-one, (2S)-2-[(S)-(2-fluorophenyl)(hydroxy)methyl]-4-benzylmorpholin-3-one, (2R)-2-[(S)-(2-fluorophenyl)(hydroxy)methyl]-4-benzylmorpholin-3-one and (2S)-2-[(R)-(2-fluorophenyl)(hydroxy)methyl]-4-benzylmorpholin-3-one (12.0g, 0.038mol) in dry THF (80ml) under nitrogen at room temperature was added a solution of borane in THF (1M, 150ml). The solution was heated at 60°C for ca. 4h then at room temperature overnight. Cooled solution to 0°C and added dropwise methanol (68ml) followed by 1NHCl (68ml). The resulting mixture was heated at 60°C for 1h, cooled and concentrated *in vacuo*. The precipitate was removed by filtration and the filtrate made basic with aqueous sodium carbonate. Extracted with diethyl ether (3x), extracts washed with water and brine, dried over magnesium sulphate, filtered and evaporated to an oil. The crude oil was purified and partially separated by flash chromatography on silica eluting with heptane/ethyl acetate (40/60 to 25/75) to give the product as a colourless oil (0.713g).

iii) (R)-[2-fluorophenyl][(2S)-4-benzylmorpholin-2-yl]methyl methanesulphonate and (S)-[2-fluorophenyl][(2R)-4-benzylmorpholin-2-yl]methyl methanesulphonate



To a stirred solution of (R)-[2-fluorophenyl][(2S)-4-benzylmorpholin-2-yl]methanol and (S)-[2-fluorophenyl][(2R)-4-benzylmorpholin-2-yl]methanol (465mg, 1.54mmol) in dry dichloromethane (10ml) at room temperature under nitrogen was added triethylamine (202mg, 2.0mmol) and methanesulphonyl chloride (177mg, 1.54mmol). After 15h, evaporated to an oil and purified by flash chromatography on silica eluting with ethyl acetate/heptane (1/1) to give the product mesylate as a colourless oil (445mg).

iv) (2R)-2-((R)-[2-fluorophenyl]{[2-methoxyphenyl]thio}methyl)-4-benzylmorpholine and (2S)-2-((S)-[2-fluorophenyl]{[2-methoxyphenyl]thio}methyl)-4-benzylmorpholine

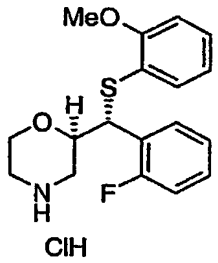


To a stirred suspension of (R)-[2-fluorophenyl][(2S)-4-benzylmorpholin-2-yl]methyl methanesulphonate and (S)-[2-fluorophenyl][(2R)-4-benzylmorpholin-2-yl]methyl methanesulphonate (445mg, 1.17mmol) and anhydrous potassium carbonate (0.97g, 7.02mmol) in dry degassed DMF (8ml) under nitrogen at room temperature was added 2-methoxybenzenethiol (0.82g, 5.87mmol). After stirring at room temperature for 18h, diluted with water and extracted with diethyl ether (2x). The extracts were washed with 2NaOH, water and brine, dried over magnesium sulphate, filtered and evaporated to an oil.

After purification by flash column chromatography (eluent: heptane/ethyl acetate 80/20 [v/v]) the title product was obtained as a colourless oil (357 mg); MW 423.55;

$C_{25}H_{26}FNO_2S$; ^1H NMR ($CDCl_3$): 6.65-7.5 (13H, m), 4.9 (1H, d, 7 Hz), 3.9-4.05 (2H, m), 3.8 (3H, s), 3.6 (1H, dt, 8 Hz and 1 Hz), 3.45 (1H, d, 13.1 Hz), 3.15 (1H, d, 13.1 Hz), 2.60 (2H, t, 8 Hz), 2.05-2.2 (2H, m); FIA: *m/z* 424 $[M+H]^+$.

v) (2R)-2-((R)-(2-Fluorophenyl){[2-methoxyphenyl]thio}methyl)morpholine hydrochloride



Reaction of the mixture of (2R)-2-((R)-[2-fluorophenyl]{[2-methoxyphenyl]thio}methyl)-4-benzylmorpholine and (2S)-2-((S)-[2-fluorophenyl]{[2-methoxyphenyl]thio}methyl)-4-benzylmorpholine (430 mg, 1.02 mmol) following procedure described in EXAMPLE 1(iv) gave a colourless oil (340 mg, 90% yield) from which the first eluting enantiomer was obtained after chiral chromatography on a Chiralcel-OD column eluant heptane/ethanol/dimethylethylamine (40/60/0.2): Rt 10.41 min. LC purity = 98.6 (UV_{254nm}); MW 333.43; $C_{18}H_{20}FNOS$.; FIA: *m/z* 334 $[M+H]^+$. This was converted into the hydrochloride salt. ^1H NMR ($CDCl_3$) freebase: 7.2-7.3 (1H, m), 6.85-7.2 (8H, m), 4.85 (1H, d, 8 Hz), 3.95-4.15 (2H, m), 3.85-3.9 (3H, m), 3.7 (1H, dt, 1 Hz and 7 Hz), 2.6-3.0 (4H, m).

EXAMPLE 3

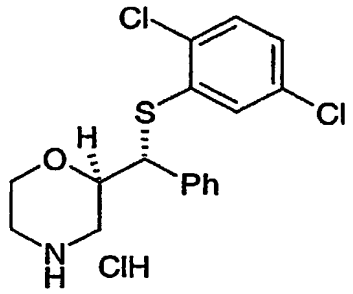
(2R)-2-((R)-[2,5-dichlorophenyl][phenylthio]methyl)morpholine hydrochloride

i) (2R)-2-((R)-[2,5-dichlorophenyl][phenylthio]methyl)-4-benzylmorpholine

Reacted (2R)-2-[(S)-bromo(phenyl)methyl]-4-benzylmorpholine (150mg, 0.43mmol) (see example 8(v)method 2), 2,5-dichlorobenzenethiol (233mg, 1.30mmol) and anhydrous potassium carbonate (71mg, 0.52mmol) following example 2(iv). The

reaction mixture was purified directly by SCX chromatography eluting with ammonia/methanol (ca.3M) to give the product as an oil (174mg).

ii) (2R)-2-((R)-[2,5-dichlorophenyl][phenylthio]methyl)morpholine hydrochloride



Debenzylation of (2R)-2-((R)-[2,5-dichlorophenyl][phenylthio]methyl)-4-benzylmorpholine (174mg, 0.39mmol) with polymer supported Hunig's base (0.20g, 0.78mmol) and α-chloroethyl chloroformate (111mg, 0.78mmol) following the procedure described in example 1(iv) gave after SCX chromatography the product as an oil (136mg).

NMR ($CDCl_3$) 7.31-7.14 (7H, m), 7.00 (1H, d), 4.41 (1H, d), 4.06-3.98 (1H, m), 3.90-3.82 (1H, m), 3.7-3.6 (1H, m), 2.94-2.76 (2H, m), 2.65 (2H, d). *m/z* [M+H] 354/6/8.

Crystallised as the HCl salt from ethanol and diethyl ether.

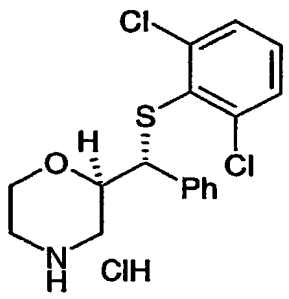
EXAMPLE 4

(2R)-2-((R)-[2,6-dichlorophenyl][phenylthio]methyl)morpholine hydrochloride

i) (2R)-2-((R)-[2,6-dichlorophenyl][phenylthio]methyl)-4-benzylmorpholine

Reacted (2R)-2-[(S)-bromo(phenyl)methyl]-4-benzylmorpholine (200mg, 0.58mmol) (see example 8(iv)), 2,6-dichlorobenzenethiol (130mg, 0.70mmol) and anhydrous potassium carbonate (97mg, 0.70mmol) following example 2(iv). The reaction mixture was purified directly by SCX chromatography eluting with ammonia/methanol (ca.3M) to give the product as an oil (230mg).

ii) *(2R)-2-((R)-[2,6-dichlorophenyl][phenylthio]methyl)morpholine hydrochloride*

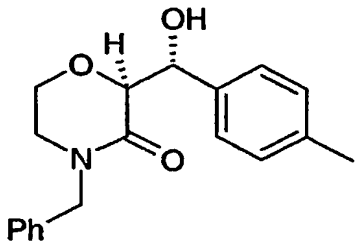


Stirred (2R)-2-((R)-[2,6-dichlorophenyl][phenylthio]methyl)-4-benzylmorpholine (230mg, 0.52mmol) with solid supported Hunig's base (270mg, 1.04mmol) and α-chloroethyl chloroformate (152mg, 1.04mmol) in dichloromethane (4ml) at room temperature under nitrogen for 3h. Filtered and concentrated *in vacuo* , dissolved oil in methanol and stirred at room temperature for 1h. Evaporated to give a colourless solid. NMR (MeOH) 7.32-7.12 (8H, m), 4.62 (1H, d), 4.31-4.22 (1H, m), 4.16-4.06 (1H, m), 3.91-3.80 (1H, m), 3.2-2.9 (4H, m).

EXAMPLE 5

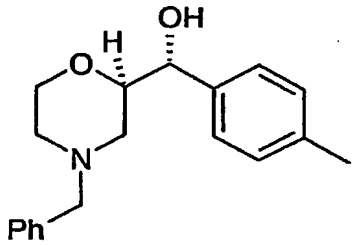
(2R)-2-((R)-[4-methylphenyl]{[2-methoxyphenyl]thio}methyl)morpholine hydrochloride

i) (2R)-2-[(S)-(4-methylphenyl)(hydroxy)methyl]-4-benzylmorpholin-3-one and (2S)-2-[(R)-(4-methylphenyl)(hydroxy)methyl]-4-benzylmorpholin-3-one



To a stirred solution of (+/-)-4-benzylmorpholin-3-one (4.06 g, 21.3 mmol) in anhydrous THF (25 ml) under nitrogen at -80°C was added lithium diisopropylamide (2.0M, 19.5 ml) solution in heptane/THF/ethylbenzene dropwise, whilst maintaining the reaction temperature below -65°C. The resulting solution was stirred for a further 30 minutes at -78°C, before being slowly added over approximately 45 minutes to a solution of 4-methylbenzaldehyde (3.07g, 25.51 mmol) in anhydrous THF (15 ml) under nitrogen at -78°C, whilst again maintaining the reaction temperature below -75°C. The resulting yellow solution was stirred at -78°C for 0.5 hour, before being allowed to warm to room temperature. The reaction mixture was cautiously quenched by addition of saturated ammonium chloride solution (50 ml) and the THF was evaporated *in vacuo* from the mixture. The resulting cloudy aqueous solution was extracted with dichloromethane, and the organic extracts were combined, washed with brine, dried over magnesium sulphate, filtered and the dichloromethane evaporated *in vacuo* to give a thick red oil (9.35 g). After purification by flash column chromatography (eluent: ethyl acetate/hexane 30/70 to 70/30 gradient [v/v]) the colourless oil obtained was triturated with hexane followed by hot cyclohexane to give after successive decanting of supernatant and drying the product as a colourless solid (2.46g).

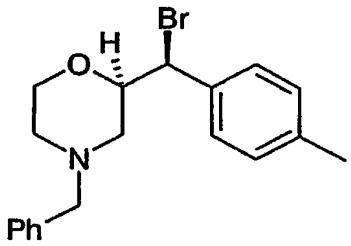
ii) *(S)-[4-methylphenyl][(2S)-4-benzylmorpholin-2-yl]methanol and (R)-[4-methylphenyl][(2R)-4-benzylmorpholin-2-yl]methanol*



The product was prepared from (2R)-2-[(S)-(4-methylphenyl)(hydroxy)methyl]-4-benzylmorpholin-3-one and (2S)-2-[(R)-(4-methylphenyl)(hydroxy)methyl]-4-benzylmorpholin-3-one (2.50g, 8.04mmol) following the procedure described in

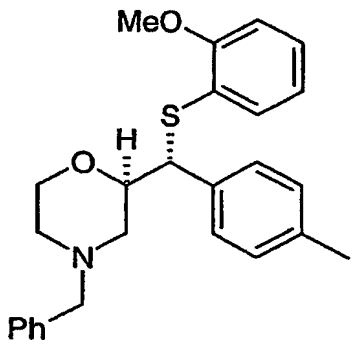
EXAMPLE 2(ii). The oil was purified by flash chromatography on silica eluting with ethyl acetate/heptane gradient 30/70 to 70/30 to give required product as an oil (1.16g).

iii) *(2R)-2-[(S)-bromo(4-methylphenyl)methyl]-4-benzylmorpholine and (2S)-2-[(R)-bromo(4-methylphenyl)methyl]-4-benzylmorpholine*



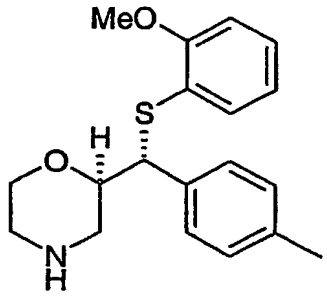
To a stirred solution of (S)-[4-methylphenyl][(2S)-4-benzylmorpholin-2-yl]methanol and (R)-[4-methylphenyl][(2R)-4-benzylmorpholin-2-yl]methanol (1.16g, 3.91mmol) and triphenylphosphine (1.54g, 5.87mmol) in dry dichloromethane was added dropwise a solution of carbon tetrabromide (1.95g, 5.87mmol) in dichloromethane over a period of 10min. Further triphenylphosphine (0.5eq) and carbon tetrabromide (0.5eq) were added after 0.5h. Quenched reaction mixture after 2h with saturated aqueous sodium bicarbonate. Extracted with dichloromethane, dried extracts over magnesium sulphate, filtered and evaporated to a red oil. Triturated oil with diethyl ether, filtered and evaporated to a yellow oily solid. The oil was purified by flash chromatography on silica eluting with ethyl acetate/heptane 20/80 to give the product as an oil (0.61g)

iv) (2R)-2-((R)-[4-methylphenyl][[2-methoxyphenyl]thio]methyl)-4-benzylmorpholine and (2S)-2-((S)-[4-methylphenyl][[2-methoxyphenyl]thio]methyl)-4-benzylmorpholine



Reacted (2R)-2-[(S)-bromo(4-methylphenyl)methyl]-4-benzylmorpholine and (2S)-2-[(R)-bromo(4-methylphenyl)methyl]-4-benzylmorpholine (340mg, 0.94mmol), 2-methoxybenzenethiol (161mg, 1.13mmol) and anhydrous potassium carbonate (160mg, 1.13mmol) following procedure described in example 2(iv). The crude oil was purified by flash chromatography on silica eluting with ethyl acetate/heptane 20/80 to give the product as an oil (0.21g).

v) *(2R)-2-((R)-(4-methylphenyl){[2-methoxyphenyl]thio}methyl)morpholine hydrochloride*



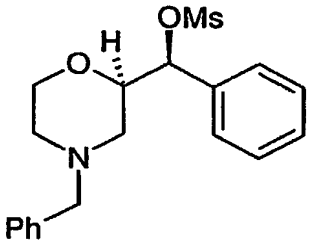
Debenzylation of (2R)-2-((R)-[4-methylphenyl]{[2-methoxyphenyl]thio}methyl)-4-benzylmorpholine and (2S)-2-((S)-[4-methylphenyl]{[2-methoxyphenyl]thio}methyl)-4-benzylmorpholine (210 mg, 0.50 mmol) following procedure described in EXAMPLE 1(iv) but at room temperature gave a colourless oil (180 mg) from which the first eluting enantiomer was obtained after chiral chromatography on a Chiralcel-OD column , elutuant heptane/isopropanol/dimethylethylamine (20/80/0.2) Rt 9.70min. The oil was dissolved in dichloromethane and HCl/diethyl ether added to give the title compound as

the hydrochloride salt (36mg). NMR (DMSO) 9.20 (2H, br. s), 7.24-7.08 (6H, m), 6.92 (1H, d), 6.89 (1H, t), 4.60 (1H, d), 4.09-3.97 (2H, m), 3.80 (3H, s), 3.78-3.66 (1H, m), 3.20-3.13 (1H, m), 3.04-2.90 (3H, m), 2.24 (3H, s).

EXAMPLE 6

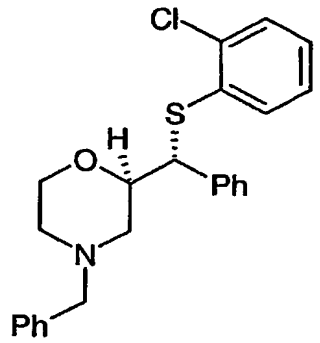
(2R)-2-((R)-[phenyl][2-chlorophenylthio]methyl)morpholine hydrochloride

i) *(R)-[Phenyl][(2S)-4-benzylmorpholin-2-yl]methyl methanesulphonate and (S)-[Phenyl][(2R)-4-benzylmorpholin-2-yl]methyl methanesulphonate*



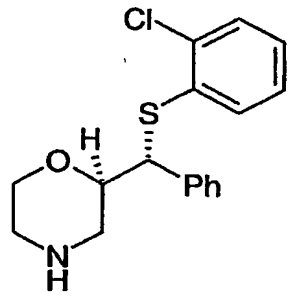
To a stirred solution of (R)-[phenyl][(2S)-4-benzylmorpholin-2-yl]methanol and (S)-[phenyl][(2R)-4-benzylmorpholin-2-yl]methanol (2.0g, 7.06mmol) in dry dichloromethane (24ml) at room temperature under nitrogen was added triethylamine (0.78g, 7.77mmol) and methanesulphonyl chloride (0.89g, 7.77mmol). After stirring overnight at room temperature, the reaction mixture was diluted with diethyl ether and filtered. The filtrate was evaporated to dryness to give an orange oil (2.5g).

ii) *(2R)-2-((R)-[phenyl][[2-chlorophenyl]thio]methyl)-4-benzylmorpholine and (2S)-2-((S)-[phenyl][[2-chlorophenyl]thio]methyl)-4-benzylmorpholine*



To a stirred suspension of (R)-[phenyl][(2S)-4-benzylmorpholin-2-yl]methyl methanesulphonate and (S)-[phenyl][(2R)-4-benzylmorpholin-2-yl]methyl methanesulphonate (790mg, 2.19mmol) and anhydrous potassium carbonate (1.50g, 10.95mmol) in dry degassed DMF (3ml) under nitrogen at room temperature was added 2-chlorobenzenethiol (1.58g, 10.95mmol). After stirring at room temperature for 18h, diluted with water and extracted with dichloromethane (2x). The extracts were washed with 2N NaOH, water and brine, dried over magnesium sulphate, filtered and evaporated to an oil. After purification by flash column chromatography (eluent: heptane/ethyl acetate 100/0 to 70/30 [v/v]) the product was obtained as a colourless oil (0.26g)

iii) *(2R)-2-((R)-[phenyl][2-chlorophenylthio]methyl)morpholine hydrochloride*



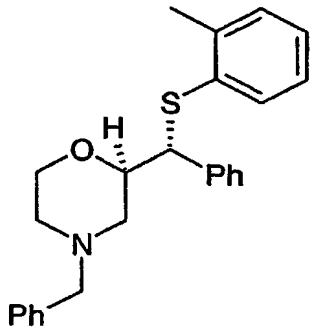
Debenzylation of (2R)-2-((R)-[phenyl]{[2-chlorophenyl]thio}methyl)-4-benzylmorpholine and (2S)-2-((S)-[phenyl]{[2-chlorophenyl]thio}methyl)-4-benzylmorpholine (250 mg, 0.61 mmol) following procedure described in EXAMPLE 1(iv) but at room temperature gave a colourless oil (190 mg) from which the first eluting enantiomer was obtained after chiral chromatography on a ChiralPak-AD column eluant

heptane/ethanol/dimethylethylamine (85/15/0.2) Rt 7.55min. NMR (DMSO) 9.34 (2H, br. s), 7.31-7.00 (9H,m), 4.68 (1H, d), 4.09-3.90 (1H, m), 3.98-3.87 (1H, m), 3.69-3.58 (1H, m), 3.10-3.01 (1H, m), 2.90-2.79 (3H, m). Converted to the title product hydrochloride salt.

EXAMPLE 7

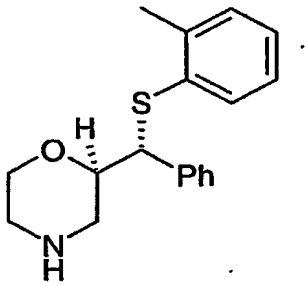
(2R)-2-((R)-[phenyl][2-methylphenylthio]methyl)morpholine hydrochloride

i) (2R)-2-((R)-[phenyl]{[2-methylphenyl]thio}methyl)-4-benzylmorpholine and (2S)-2-((S)-[phenyl]{[2-methylphenyl]thio}methyl)-4-benzylmorpholine



The product was prepared as an oil (0.22g) from(R)-[phenyl][(2S)-4-benzylmorpholin-2-yl]methyl methanesulphonate and (S)-[phenyl][(2R)-4-benzylmorpholin-2-yl]methyl methanesulphonate (0.49g, 1.46mmol), 2-methylbenzenethiol (0.22g, 1.75mmol) and potassium carbonate (0.24g, 1.75mmol) following the procedure described in EXAMPLE 6(ii)

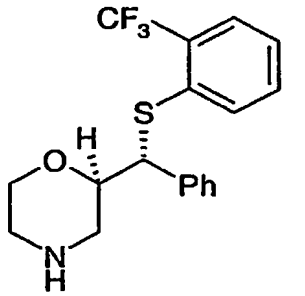
ii) (2R)-2-((R)-[phenyl][2-methylphenylthio]methyl)morpholine hydrochloride



Debenzylation of (2R)-2-((R)-[phenyl]{[2-methylphenyl]thio}methyl)-4-benzylmorpholine and (2S)-2-((S)-[phenyl]{[2-methylphenyl]thio}methyl)-4-benzylmorpholine (210 mg, 0.54 mmol) following procedure described in EXAMPLE 1(iv) but at room temperature gave a colourless oil (180 mg) from which the first eluting enantiomer was obtained after chiral chromatography on a ChiralPak-OJ column eluant heptane/ethanol/dimethylethylamine (40/60/0.2) Rt 8.86min. This was converted to the title product hydrochloride salt and crystallised from isopropanol/methanol. NMR ($CDCl_3$) 10.06 (2H, br. s), 7.20-6.93 (9H, m), 4.35-4.27 (1H, m), 4.10-3.93 (3H, m), 3.22-3.11 (2H, m), 3.03-2.86 (2H, m), 2.28 (3H, s).

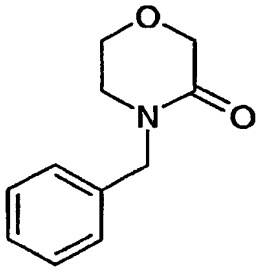
EXAMPLE 8

(2R)-2-((R)-[phenyl][2-trifluoromethylphenylthio]methyl)morpholine hydrochloride



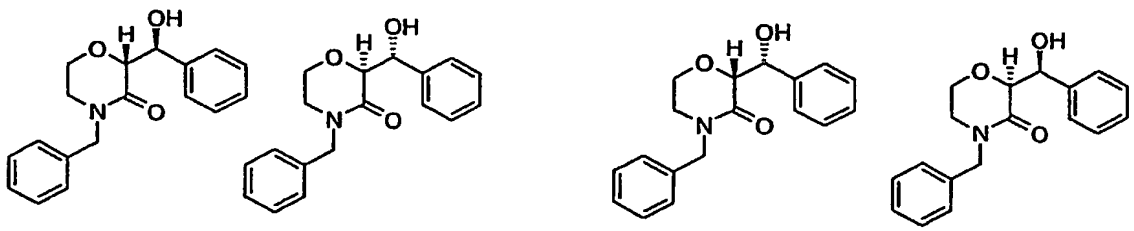
Method 1

(i) *4-Benzylmorpholin-3-one*



A solution of *N*-benzyl-*N*-(2-hydroxyethyl)chloroacetamide (1.0 eq., 627.7 g, 2.759 mol) in tert-butanol (0.9 L) was stirred under nitrogen while warming to 25-30 °C. A 1.0 M solution of potassium tert-butoxide in tert-butanol (1.05 eq., 2.897 L, 2.897 mol) was added over 2 hours, maintaining the reaction temperature between 30 and 32 °C. The reaction mixture was stirred at 27-28 °C for 90 minutes. When TLC showed the reaction to be complete, ice-cold water (6 L) was added and the resultant cloudy solution extracted with EtOAc (1 x 3 L, 2 x 1.5 L). The combined organic layers were washed with brine (2 x 3 L), dried over MgSO4 and evaporated *in vacuo* to give a light brown oil (441 g, 84% yield), which was used in the next stage without further purification; MW 191.23; C11H13NO2; Rf 0.52 (80% EtOAc, 20% hexane); 1H NMR (CDCl3): 7.40-7.29 (5H, m), 4.67 (2H, s), 4.28 (2H, s), 3.87 (2H, t, 5.4 Hz), 3.31 (2H, t, 5.4 Hz); LCMS: m/z 192 [M+H]+ @ Rt 1.00 min (single major peak).

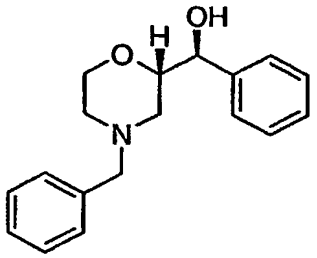
(ii) (2R)-4-benzyl-2-[(S)-hydroxy(phenyl)methyl]morpholin-3-one, (2S)-4-benzyl-2-[(R)-hydroxy(phenyl)methyl]morpholin-3-one and (2R)-4-benzyl-2-[(R)-hydroxy(phenyl)methyl]morpholin-3-one, (2S)-4-benzyl-2-[(S)-hydroxy(phenyl)methyl]morpholin-3-one

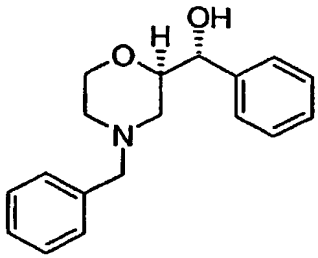


To a stirred solution of 4-benzylmorpholin-3-one (5.02 g, 26 mmol) in anhydrous THF (25 ml) under nitrogen at -78°C was added a 2 M. solution of LDA in heptane/THF/ethylbenzene (1.5 eq., 39 mmol, 19.5 ml) over approximately 20 minutes, whilst maintaining the reaction temperature below -75°C. The resulting brown solution was stirred for a further 30 minutes at -78°C , before being slowly added over approximately 30 minutes to a solution of benzaldehyde (1.2 eq., 3.34 g, 31 mmol) in anhydrous THF (15 ml) under nitrogen at -78°C , whilst again maintaining the reaction temperature below -75°C . The resulting yellow solution was stirred at -78°C for 1 hour, before being allowed to warm to room temperature slowly over 1 hour. The reaction mixture was cautiously quenched by addition of saturated ammonium chloride solution (50 ml) and the THF was evaporated *in vacuo* from the mixture. The resulting cloudy aqueous solution was extracted with DCM (3 x 50 ml), and the organic extracts were combined, washed with brine (50 ml), dried over Na_2SO_4 and the DCM evaporated *in vacuo* to give a thick brown oil (9.2 g), which partially crystallised on standing. The mixture of diastereoisomeric alcohols was purified and separated by flash column chromatography using gradient elution (from 10% EtOAc, 90% DCM to 20% EtOAc, 80% DCM), which gave (2R)-4-benzyl-2-[(S)-hydroxy(phenyl)methyl]morpholin-3-one and (2S)-4-benzyl-2-[(R)-hydroxy(phenyl)methyl]morpholin-3-one as light red crystals (2.461 g, 31% yield); MW 297.36; C18H19NO3; Rf 0.40 (50% EtOAc, 50% hexane); 1H NMR (CDCl3): 7.41-7.36 (2H, m), 7.31-7.16 (6H, m), 6.91-6.86 (2H, m), 5.14 (1H, d, J 3.5 Hz), 4.71 (1H ,d, 14.5 Hz), 4.48 (1H, d, J 3.5 Hz), 4.25 (1H, d, 14.5 Hz), 4.20 (1H, br. s), 3.89 (1H, ddd, 11.7 Hz, 2.5 Hz, 2.0 Hz), 3.67 (1H, dt, 11.2 Hz, 3.4 Hz), 3.16 (1H, dt, 12.0 Hz, 4.0 Hz), 2.86 (1H, br. d, 12.0 Hz); LCMS: m/z 298 [M+H]+ @ Rt 1.24 min (single major peak). This reaction was performed on scales from 200 mg to 5 g (yield range 20 to 40%). (2R)-4-benzyl-2-[(R)-hydroxy(phenyl)methyl]morpholin-3-one and (2S)-4-benzyl-2-[(S)-hydroxy(phenyl)methyl]morpholin-3-one diastereoisomer was isolated as a brown solid (1.42 g) contaminated with *N*-benzylmorpholin-3-one. Trituration with EtOAc afforded the pure compound as a white solid (0.484 g, 6% yield); MW 297.36; C18H19NO3; Rf 0.23 (50% EtOAc, 50% hexane); 1H NMR (CDCl3): 7.61-7.55 (2H, m), 7.50-7.36 (6H, m), 7.31-7.25 (2H, m), 5.21 (1H, d, 2.3 Hz), 5.09 (1H, d, J 7.7 Hz, 2.3 Hz), 4.73 (2H, s, s Hz), 4.37 (1H, d, J 7.7 Hz), 4.01(1H, ddd, 12.0 Hz, 2.6 Hz,

1.9 Hz), 3.77 (1H, dt, 11.0 Hz, 3.5 Hz), 3.50 (1H, dt, 12.0 Hz, 4.0 Hz), 3.16 (1H, br. d, 12.0 Hz); LCMS: m/z 298 [M+H]+ @ Rt 1.24 min (single major peak).

(iii) (S)-[(2S)-4-benzylmorpholinyl](phenyl)methanol and (R)-[(2R)-4-benzylmorpholinyl](phenyl)methanol

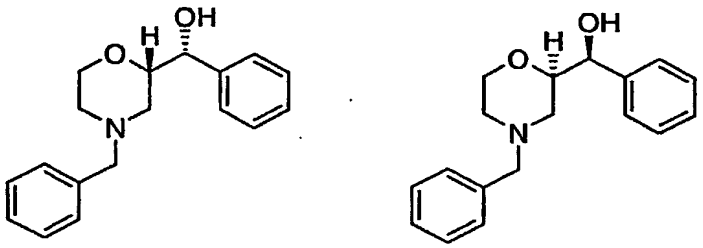




To a solution of (2R)-4-benzyl-2-[(S)-hydroxy(phenyl)methyl]morpholin-3-one and (2S)-4-benzyl-2-[(R)-hydroxy(phenyl)methyl]morpholin-3-one (326 mg, 1.1 mmol) in anhydrous THF (5 ml) under nitrogen at room temperature was slowly added a 1 M solution of borane in THF (4 eq., 4.4 ml, 4.4 mmol). The solution was stirred at 60°C for 2 hours. After cooling down to room temperature, dry methanol (2 ml) was slowly added to quench excess borane reagent. 1 M. Aqueous hydrochloric acid solution (2 ml) was added and the reaction mixture was heated to 60°C for 1 hour. The organic solvents were evaporated *in vacuo* and the concentrated solution was poured onto 1 M aqueous potassium carbonate solution (10 ml) and extracted with diethyl ether (2 x 20 ml). The combined organic layers were washed with brine (20 ml), water (20 ml), dried over MgSO4 and concentrated *in vacuo*. The resultant oil was purified by flash column chromatography (90% hexane, 9% EtOAc, 1% NEt3) to give a viscous oil (189 mg, 60% yield); MW 283.37; C18H21NO2; Rf 0.42 (90% EtOAc, 10% hexane); 1H NMR (CDCl3): 7.45-7.32 (10H, m), 4.67 (1H, d, 7.3 Hz), 4.03 (1H, dt, 11.4 Hz, 2.7 Hz), 3.86-3.73 (2H, m), 3.64 (1H, d, 13.2 Hz), 3.39 (1H, d, 13.2 Hz), 3.30 (1H, br. s), 2.68 (1H, d, 12.7 Hz), 2.56 (1H, d, 10.9 Hz), 2.28-2.15 (2H, m); LCMS: m/z 284 [M+H]+ @ Rt 0.95 min (single major peak).

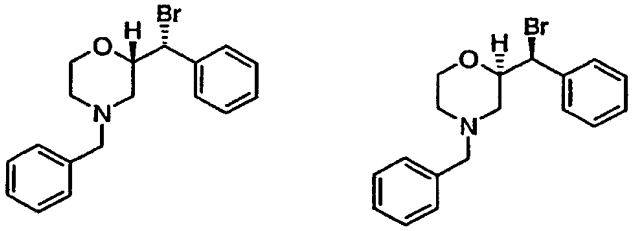
This reaction was performed on scales from 50 mg to 1.5 g (yield range = 50 to 84%).

(iv) (R)-[(2S)-4-benzylmorpholinyl](phenyl)methanol and (S)-[(2R)-4-benzylmorpholinyl](phenyl)methanol



Using the procedure described in Example 8(iii) starting from (2R)-4-benzyl-2-[(R)-hydroxy(phenyl)methyl]-morpholin-3-one and (2S)-4-benzyl-2-[(S)-hydroxy(phenyl)methyl]-morpholin-3-one (135 mg, 0.51 mmol) the reaction and subsequent purification yielded a viscous oil (98 mg, 68% yield); MW 283.37; $C_{18}H_{21}NO_2$; Rf 0.52 (100% EtOAc); 1H NMR (CDCl3): 7.28-7.17 (10H, m), 4.80 (1H, d, 4.0 Hz), 3.88 (1H, dt, 11.4 Hz, 3.0 Hz), 3.72 (1H, m), 3.68-3.61 (1H, m), 3.50 (1H, d, 13 Hz), 3.25 (1H, d, 13 Hz), 2.52 (2H, br. t, 12.0 Hz), 2.17 (1H, t, 11 Hz), 2.08 (1H, td, 11 Hz, 3.0 Hz), OH not observed; LCMS: m/z 284 [M+H]+ @ Rt 0.98 min (single major peak). This reaction was performed on scales from 100 to 400 mg (yield range = 60 to 93%).

(v) (2R)-4-benzyl-2-[(S)-bromo(phenyl)methyl]morpholine and (2S)-4-benzyl-2-[(R)-bromo(phenyl)methyl]morpholine

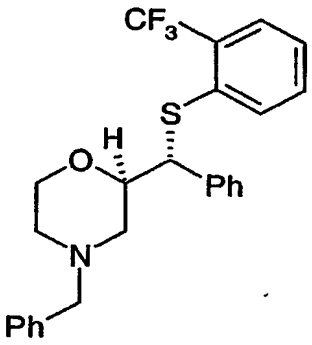


To a solution of (S)-[(2S)-4-benzylmorpholinyl](phenyl)methanol and (R)-[(2R)-4-benzylmorpholinyl](phenyl)methanol (10.27 g, 36.29 mmol) in anhydrous dichloromethane (150 ml) under nitrogen at room temperature was added freshly recrystallised triphenylphosphine (1.4 eq., 13.310 g, 50.80 mmol) followed by carbon tetrabromide (1.4 eq., 16.849 g, 50.80 mmol) as a solution in anhydrous dichloromethane (50 ml). After 15 minutes the reaction mixture was diluted with dichloromethane (100 ml)

and washed with saturated aqueous sodium hydrogencarbonate solution (150 ml), brine (150 ml), dried over MgSO4 and concentrated *in vacuo* to give an orange oil (42.0 g). To the orange oil was added diethyl ether (200 ml) and the resulting suspension was sonicated for 30 minutes. The solvent was decanted and the process repeated with a further portion of diethyl ether (200 ml). The combined ethereal extracts were concentrated *in vacuo* to yield an orange solid (22.0 g) which was purified by flash column chromatography (10% EtOAc : 89.5% Hexane, 0.5% Triethylamine) to give a white solid (7.20 g, 58% yield). Alternative Work-up: The reaction mixture was poured onto a silica (160 g) filtration pad which was washed using suction with dichloromethane (14 x 250 ml). Stripping this filtrate *in vacuo* gave crude product (16.0 g, 131% uncorrected). This was purified by flash column chromatography (5% EtOAc : 94.5% Hexane : 0.5% Triethylamine to 10% EtOAc : 89.5% Hexane : 0.5% Triethylamine) to give a white solid (6.05 g, 50% yield); MW 346.27; C18H20BrNO; Rf 0.76 (70% EtOAc, 30% hexane); 1H NMR (CDCl3): 7.39-7.14 (10H, m), 4.83 (1H, d, 7.4 Hz), 4.01 (1H, br. t, 8.3 Hz), 3.73 (1H, br. d, 11.1 Hz), 3.60-3.48 (2H, m), 3.39 (1H, d, 12 Hz), 3.20 (1H, d, 11.4 Hz), 2.50 (1H, d, 10.4 Hz), 2.07 (2H, t, 10.9 Hz); LCMS: m/z 348/346 [M+H]+ @ Rt 1.20 min (single major peak). This reaction was performed on scales from 100 to 400 mg (yield range = 60 to 93%).

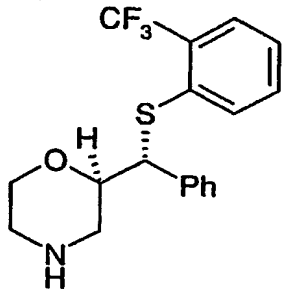
A sample of racemic (2R)-4-benzyl-2-[(S)-bromo(phenyl)methyl]morpholine and (2S)-4-benzyl-2-[(R)-bromo(phenyl)methyl]morpholine (6.02g) was separated by preparative chiral chromatography (Chiralcel-AD 1kg column, ethanol: dimethylethylamine 100: 0.3) to give the first eluting enantiomer Rt 23.4min as an off-white solid (2.89g) of (2R)-4-benzyl-2-[(S)-bromo(phenyl)methyl]morpholine and the second eluting enantiomer Rt 28.9min as an off-white solid (2.89g) of (2S)-4-benzyl-2-[(R)-bromo(phenyl)methyl]morpholine (2.21g)

vi) (2R)-2-((R)-[phenyl]{[2-trifluoromethylphenyl]thio}methyl)-4-benzylmorpholine and (2S)-2-((S)-[phenyl]{[2-trifluoromethylphenyl]thio}methyl)-4-benzylmorpholine



To a stirred solution of 2-trifluoromethylthiophenol (2.469g, 13.86mmol) and (2R)-2[(S)-bromo(4-methylphenyl)methyl)-4-benzylmorpholine and (2S)-2[(R)-bromo(4-methylphenyl)methyl)-4-benzylmorpholine (4.0g, 11.55mmol) in anhydrous DMF (60ml) at room temperature under nitrogen was added cesium carbonate (4.14g, 12.71g). The reaction mixture was heated at 95°C for 1h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, then washed sequentially with water, brine, dried over magnesium sulphate, filtered and evaporated to a brown oil. The oil was purified by flash column chromatography (eluent: hexane/ethyl acetate gradient 100 to 90/10 [v/v]) to give a yellow oil (4.83 g, 94% yield); MW 444; $C_{25}H_{24}F_3NOS$; ^1H NMR ($CDCl_3$): 7.60 (1H, dd, 7.2 Hz, 1.4 Hz), 7.17-7.39 (13H, m), 4.50 (1H, d, 7.2 Hz), 3.97-4.12 (2H, m), 3.73 (1H, dt, 9.7 Hz, 2.3 Hz), 3.59 (1H, d, 12.6 Hz), 3.37 (1H, d, 12.6 Hz), 2.57-2.68 (2H, m); 2.18-2.38 (2H, m); LCMS (2.5 minutes method): m/z 445 [M+H]+ @ Rt 1.50 min.

vii) (2R)-2-((R)-[phenyl][2-trifluoromethylphenylthio]methyl)morpholine hydrochloride



The title compound was obtained from (2R)-2-((R)-[phenyl]{[2-trifluoromethylphenyl]thio}methyl)-4-benzylmorpholine and (2S)-2-((S)-[phenyl]{[2-

trifluoromethylphenyl]thio}methyl)-4-benzylmorpholine (5.25 g, 11.84 mmol), solid supported Hunig's base (Argonaut, 3.56 mmol/g, 6.64 g, 23.67 mmol, 2 eq.) and α-chloroethyl chloroformate (3.83 ml, 35.51 mmol, 3 eq.) in anhydrous dichloromethane (75 ml) at 40°C following the method described in example 1(iv). After evaporation of the methanol solution a light brown solid (5.60 g) was obtained which was recrystallised from iso-propanol to give the hydrochloride salt as fine white needles. The hydrochloride salt was suspended in ethyl acetate and washed with an aqueous solution of sodium hydroxide (50 ml of a 1M solution). The organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to yield the free amine as a colourless oil (3.10 g, 74% yield); MW 353.41; $C_{18}H_{18}F_3NOS$; ^1H NMR ($CDCl_3$): 7.46 (1H, d, 7.7 Hz), 7.24 (1H, d, 7.3 Hz), 7.05-7.2 (7H, m), 4.28 (1H, d, 7.7 Hz), 3.92 (1H, d, 11.4 Hz), 3.80 (1H, q, 7.0 Hz), 3.58 (1H, dt, 1.82 Hz, 11.4 Hz), 2.69-2.87 (2H, m), 2.59 (2H, d, 6.0 Hz), 2.13-1.90 (1H, br s); LCMS (10 minutes method): m/z 354 [M+H]+ @ Rt 5.26 min.

A sample of the racemic free base (1.384g) was separated by preparative chiral chromatography (Chiralpak-OJ, heptane: isopropanol: dimethylethylamine 70: 30: 0.2) to give the first eluting enantiomer Rt 9.5min (0.57g) as an oil. Redissolved in diethyl ether (20ml) and treated with ethereal hydrogen chloride (2M 0.8ml) to give a white solid (566mg, mp 240-1°C) of the title product (2R)-2-((R)-[phenyl][2-trifluoromethylphenylthio]methyl)morpholine hydrochloride.

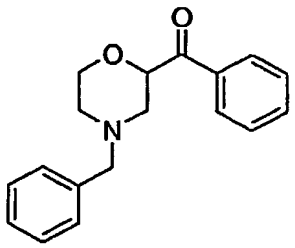
The second eluting enantiomer Rt 15.8min was obtained as an oil (0.55g) and similarly converted to the hydrochloride salt (2S)-2-((S)-[phenyl][2-trifluoromethylphenylthio]methyl)morpholine hydrochloride (556mg mp 244-5°C). A sample (20mg) was crystallised from isopropanol (2ml) allowing the solvent to evaporate slowly over several weeks. The crystals were analysed by xray crystallography to confirm the absolute stereochemistry as (S,S) for the second eluting enantiomer, data is listed in tables 1-6 herein.

Method 2

(i) 4-benzyl-morpholin-3-one

A one-liter reactor with mechanical stirring, cooled by ice bath, was charged with *N*-benzylethanolamine (172.2 g, 1.14 mol). 2-Chloroacrylonitrile (100g, 1.14 mol) was added dropwise over a period of 2 minutes. The temperature was kept between 23°C and 29°C using an ice bath, progressively replaced by a water bath at 15°C. After stirring at room temperature over night the mixture was dissolved in THF and transferred into a 2l reactor cooled to –5°C by an ice/NaCl bath. The total volume of THF equalled 1.35l. Potassium *tert*-butoxide (148g, 1.1 eq.) was added in portions over 1hour, while maintaining the temperature at 0±2°C. After 1 hour stirring at 0°C the mixture was quenched by saturated $NaHCO_3$ (500ml). The aqueous layer was extracted with diethyl ether. The organic layers were dried over $MgSO_4$ and evaporated to dryness. After percolation of the 250 g dry residue on 1 kg SiO_2 (eluent: ethyl acetate/n-heptane gradient 5/95 to 80/100 [v/v]) 4-benzyl-morpholin-3-one was obtained as a clear oil (149.8g, 65%).

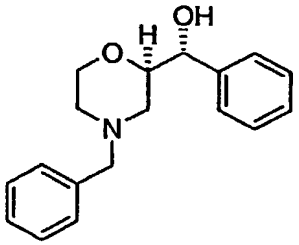
(ii) (2S)-(4-Benzyl-morpholin-2-yl)-phenyl-methanone and (2R)-(4-Benzyl-morpholin-2-yl)-phenyl-methanone



A 3l double jacket reactor was charged with 4-benzyl-morpholin-3-one (135.05 g; 1eq) and dry diethyl ether (1.4l). When Tj=0°C and Tm=1°C phenyl magnesium chloride (2M sol. in THF, 360ml, 1.08 equiv) was added dropwise over 1hour. Tm rose to 4°C and came back to 2°C at the end of the addition. Tm was progressively raised to 17.5°C within 45 minutes and the mixture stirred at this temperature for another 45 minutes. The reactor was cooled down to Tm=2°C and Tj=0°C (75 minutes) and hydrochloric acid (700ml of 5N solution) was added in two portions. Tm rose to 33°C. After some minutes, the hydrochloride salt of the ketone crystallised. When Tm=Tj=room temperature, the triphasic suspension was filtrated. The organic layer of the mother liquors, which contains impurities, was eliminated. The filtration cake was then washed with methylene chloride

(700ml). This liquor was charged in the reactor with the acid aqueous layer. Treatment of the hydrochloride salt: After drying under vacuum, 164.4 g of the hydrochloride contaminated with $MgCl_2$ were suspended in a biphasic mixture of water/methylenelchloride (500ml/800ml). The suspension was basified with aqueous sodium hydroxide (75 ml of a 30% solution) under ice bath cooling. $Mg(OH)_2$ precipitated and the aqueous layer was extracted with methylene chloride. The organic layers are filtrated on a bed of Celite 512 after adding some Celite to the layers themselves. The filtrated organic phase was dried over $MgSO_4$ and evaporated to dryness. The ketone crystallizes readily on standing (132.4g; 70%). Treatment of the mother liquors: The combined organic phases were washed with aqueous sodium hydroxide (750ml of a 2N solution). Celite 512 (160 g) was added to the suspension which was then filtrated through bed of Celite. The aqueous layer was separated and extracted with methylene chloride. The combined organic phases were dried over $MgSO_4$ and evaporated to dryness to provide 35.8 g of product enriched with unreacted nitrile. This fraction could be further purified by percolation on SiO_2.
(2S)-(4-benzyl-morpholin-2-yl)-phenyl-methanone and (2R)-(4-benzyl-morpholin-2-yl)-phenyl-methanone were separated using preparative chiral chromatography.

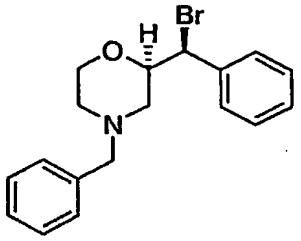
(iii) (R)-phenyl[(2R)-4-(phenylmethyl)morpholin-2-yl]methanol



To a stirred solution of (+)-DIP chloride (49.6 g, 155 mmol) in dry THF (150 ml) under nitrogen was added (2R)-(4-benzyl-morpholin-2-yl)-phenyl-methanone (16.54g, 58.89 mmol) in one portion. The reaction mixture was stirred at room temperature for 18 hours. The mixture was evaporated *in vacuo* and the crude oil taken up in methanol and absorbed onto 250g SCX-2 ion exchange resin. After elution of borane residues with methanol the product was eluted with 2M ammonia in methanol. Removal of solvent *in vacuo* yielded the product as yellow oil. (11.23g, 67%); MW 283.37; $C_{18}H_{21}NO_2$; ^1H

NMR ($CDCl_3$): 7.32-7.45 (10H, m), 4.67 (1H, d, 7.3 Hz), 4.03 (1H, dt, 11.4 Hz, 2.7 Hz), 3.86-3.73 (2H, m), 3.64 (1H, d, 13.2 Hz), 3.39 (1H, d, 13.2 Hz), 3.30 (1H, br. s), 2.68 (1H, d, 12.7 Hz), 2.56 (1H, d, 10.9 Hz), 2.28-2.15 (2H, m); LCMS: m/z 284 [M+H]+ @ Rt 0.95 min.

(v) (2R)-2-[(S)-bromo(phenyl)methyl]-4-(phenylmethyl)morpholine



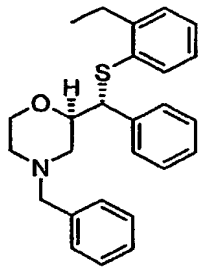
To a solution of *(R)*-phenyl[(2*R*)-4-(phenylmethyl)morpholin-2-yl]methanol (11.2g, 39.58 mmol) in anhydrous chloroform (400 ml) under nitrogen was added PPh_3Br_2 (33.41g, 79.15 mmol). The reaction mixture was heated at 60°C overnight. The mixture was allowed to cool to room temperature then washed with saturated aqueous sodium carbonate solution, dried over $MgSO_4$ and concentrated *in vacuo*. The resulting residue was purified by flash chromatography on silica (eluent: ethyl acetate:isohexane 1:4) to give a pale yellow oil. Trituration with isohexane gave (2R)-2-[(S)-bromo(phenyl)methyl]-4-(phenylmethyl)morpholine as a colourless solid (8.54g, 62%); MW 346.27; $C_{18}H_{20}BrNO$; ^1H NMR ($CDCl_3$): 7.14-7.39 (10H, m), 4.83 (1H, d, 7.4 Hz), 4.01 (1H, br. t, 8.3 Hz), 3.73 (1H, br. d, 11.1 Hz), 3.60-3.48 (2H, m), 3.39 (1H, d, 12 Hz), 3.20 (1H, d, 11.4 Hz), 2.50 (1H, d, 10.4 Hz), 2.07 (2H, t, 10.9 Hz); LCMS: (6 min method) m/z 346 [M]+ @ Rt 2.51 min.

(vi) (2R)-2-[(S)-bromo(phenyl)methyl]-4-(phenylmethyl)morpholine can then be converted to the title product (2R)-2-((R)-[phenyl][2-trifluoromethylphenylthio]methyl)morpholine hydrochloride using the above procedure in example 8 Method 1 (v) and (vi).

EXAMPLE 9

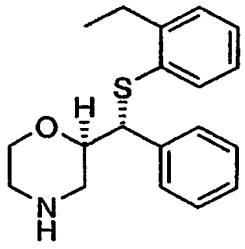
(2*R*)-2-[(*R*)-[(2-ethylphenyl)thio](phenyl)methyl]morpholine

i) (2S)-2-[(S)-[(2-ethylphenyl)thio](phenyl)methyl]-4-(phenylmethyl)morpholine and (2R)-2-[(R)-[(2-ethylphenyl)thio](phenyl)methyl]-4-(phenylmethyl)morpholine



Compound (2*S*)-2-[(*S*)-[(2-ethylphenyl)thio](phenyl)methyl]-4-(phenylmethyl)morpholine and (2*R*)-2-[(*R*)-[(2-ethylphenyl)thio](phenyl)methyl]-4-(phenylmethyl)morpholine was obtained from 2-ethyl-thiophenol (160 mg, 1.16 mmol) and (2R)-4-benzyl-2-[(S)-bromo(phenyl)methyl]morpholine and (2S)-4-benzyl-2-[(R)-bromo(phenyl)methyl]morpholine (200 mg, 0.58 mmol) following a modification of the method described in example 8(vi) in which the reaction mixture was heated to 95°C for 2 hours. After purification by flash column chromatography (eluent: ethyl acetate/hexane 9/1 [v/v]) the product was obtained as a white solid (152 mg, 65 % yield); MW 403.59; $C_{26}H_{29}NOS$; ^1H NMR ($CDCl_3$): 6.96-7.40 (14H, m), 4.22 (1H, d, 7.2 Hz), 3.96-4.01 (2H, m), 3.72 (1H, td, 11.1 Hz, 2.2 Hz), 3.52 (1H, d, 13.1 Hz), 3.32 (1H, d, 13.1 Hz), 2.68 (2H, q, 7.7 Hz), 2.59 (2H, br d, 11.7 Hz), 2.06-2.21 (2H, m), 1.12 (3H, t, 7.2 Hz); LCMS (2.5 minute method) m/z 404 [M+H]+ @ Rt 1.49 min.

ii) (2R)-2-[(R)-[(2-ethylphenyl)thio](phenyl)methyl]morpholine hydrochloride



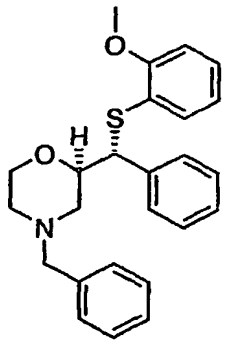
Reaction of (2*S*)-2-[(*S*)-[(2-ethylphenyl)thio](phenyl)methyl]-4-(phenylmethyl)morpholine and (2*R*)-2-[(*R*)-[(2-ethylphenyl)thio](phenyl)methyl]-4-(phenylmethyl)morpholine following the method in example 1(iv) gave a viscous yellow

oil (213.3 mg, 86% yield) from which the title product was obtained after chiral separation on chiral OD semi-preparative column; LC purity = 100% (UV254nm) / 100% (ELS); MW 313.47; $C_{19}H_{23}NOS$; ^1H NMR ($CDCl_3$): 7.17 (1H, d, 7.6 Hz), 7.12-7.05 (5H, m), 7.01 (2H, d, 3.8 Hz), 6.87-6.93 (1H, m), 4.07 (1H, d, 8.1 Hz), 3.92-3.97 (1H, m), 3.74-3.80 (1H, m), 3.59 (1H, td, 11.4 Hz, 3.0 Hz), 2.80 (1H, td, 12.4 Hz, 3.3 Hz), 2.71 (1H, br. d, 12.1 Hz), 2.63-2.54 (4H, m), 1.64 (1H, br. s), 1.04 (3H, t, 7.6 Hz); LCMS (10 minutes method): m/z 314 [M+H]+ @ Rt 5.92 min. (2*R*)-2-[(*R*)-[(2-ethylphenyl)thio](phenyl)methyl]morpholine was converted into its hydrochloride salt. MW 349.93; $C_{19}H_{23}NOS.HCl$; ^1H NMR ($CDCl_3$): 10.10 (2H, br. s), 7.13-7.28 (8H, m), 7.02-7.08 (1H, m), 4.36 (1H, br. s), 4.01-4.17 (3H, br. m), 3.16-3.31 (2H, br. m), 2.92-3.09 (2H, br. m), 2.71 (2H, q, 7.7 Hz), 1.15 (3H, t, 7.2 Hz).

EXAMPLE 10

(2*R*)-2-[(*R*)-{[2-(Methyloxy)phenyl]thio}(phenyl)methyl]morpholine hydrochloride

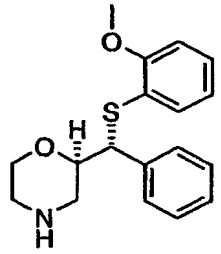
i) (2S)-2-[(S)-{[2-(Methyloxy)phenyl]thio}(phenyl)methyl]-4-(phenylmethyl)morpholine and (2R)-2-[(R)-{[2-(Methyloxy)phenyl]thio}(phenyl)methyl]-4-(phenylmethyl)morpholine



Compound (2*S*)-2-[(*S*)-{[2-(Methyloxy)phenyl]thio}(phenyl)methyl]-4-(phenylmethyl)morpholine and (2*R*)-2-[(*R*)-{[2-(Methyloxy)phenyl]thio}(phenyl)methyl]-4-(phenylmethyl)morpholine was obtained from 2-methoxy thiophenol (74 µl, 0.574 mmol) and (2R)-4-benzyl-2-[(S)-bromo(phenyl)methyl]morpholine and (2S)-4-benzyl-2-[(R)-bromo(phenyl)methyl]morpholine (181 mg, 0.522 mmol) following the method in

example 8(vi) in which the reaction was heated at 95°C for 2.5h. After purification by flash column chromatography (eluent: ethyl acetate/hexane gradient 15/85 to 25/75 [v/v]) the product was obtained as a viscous yellow oil (175 mg, 83% yield); MW 405.56; $C_{25}H_{27}NO_2S$; ^{1}H NMR ($CDCl_3$): 7.01-7.26 (12H, m), 6.58-6.63 (2H, m), 4.39 (1H, d, 7.2 Hz), 3.86-3.91 (2H, m), 3.71 (3H, s), 3.56-3.62 (1H, m), 3.42 (1H, d, 10.8 Hz); 3.21 (1H, d, 10.8 Hz), 2.46-2.52 (2H, m), 2.01-2.11 (2H, m); LCMS (10 minutes method): *m/z* 406 $[M+H]^+$ @ R_T 6.09 min.

ii) (2R)-2-[(R)-{[2-(Methyloxy)phenyl]thio}(phenyl)methyl]morpholine hydrochloride

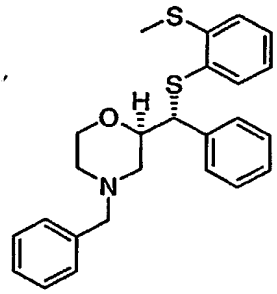


Reaction of (2*S*)-2-[(*S*)-{[2-(Methyloxy)phenyl]thio}(phenyl)methyl]-4-(phenylmethyl)morpholine and (2*R*)-2-[(*R*)-{[2-(Methyloxy)phenyl]thio}(phenyl)methyl]-4-(phenylmethyl)morpholine (100 mg, 0.25 mmol) following the method in example 1(iv) gave a viscous yellow oil (60 mg, 77% yield) from which the product was obtained after chiral separation on a Chiralcel OJ semi-preparative column. LC purity = 100%; MW 315.44; $C_{18}H_{21}NO_2S$; ^{1}H NMR ($CDCl_3$): 7.14-7.34 (7H, m), 6.74-6.84 (2H, m), 4.50 (1H, d, 8.2 Hz), 4.10 (1H, d, 10.9 Hz), 3.85-4.00 (4H, m), 3.74 (1H, dt, 1.4 Hz, 11.3 Hz), 2.82-3.02 (2H, m), 2.66-3.02 (3H, m); LCMS (10 minutes method): *m/z* 316 $[M+H]^+$ @ R_t 4.87 min. This was converted to its hydrochloride salt.

EXAMPLE 11

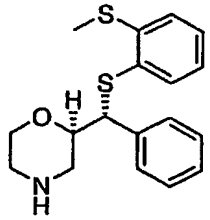
(2R)-2-[(R)-{[2-(methylthio)phenyl]thio}(phenyl)methyl]morpholine hydrochloride

i) (2R)-2-((R)-[phenyl]{[2-methylthiophenyl]thio}methyl)-4-benzylmorpholine and (2S)-2-((S)-[phenyl]{[2-methylthiophenyl]thio}methyl)-4-benzylmorpholine



To a solution of (2R)-4-benzyl-2-[(S)-bromo(phenyl)methyl]morpholine and (2S)-4-benzyl-2-[(R)-bromo(phenyl)methyl]morpholine (4.0 g, 11.55 mmol) and 2-methylsulphenyl-thiophenol (1.2 eq, 2.17 g, 13.86 mmol) in anhydrous DMF (35 ml) at room temperature under nitrogen was added cesium carbonate (1.18 eq., 14.04 g, 13.63 mmol). The mixture was heated at 50°C for 1.5 hours, allowed to cool to room temperature, taken up in methanol and treated with SCX-2 (100 g). The SCX-2 was washed with methanol. The product was obtained as a white solid (4.92 g) after SCX chromatography (eluent: ammonia/methanol 1/1 [v/v]) and removal of solvents *in vacuo*. Purification by flash column chromatography (eluent: ethyl acetate/isohexane gradient 10/90 to 30/70 [v/v]) gave a white solid (4.04 g, 86%); MW 421.63; $C_{27}H_{25}NOS_2$; ^1H NMR ($CDCl_3$): 7.03-7.15 (6H, m), 6.93-6.99 (2H, m), 6.74 (1H, td, 7.3 Hz, 1.5 Hz), 4.31 (1H, d, 7.8 Hz), 3.95 (1H, br. d, 12.1 Hz), 3.83 (1H, td, 8.1 Hz, 3.8 Hz), 3.59 (1H, td, 11.1 Hz, 2.8 Hz), 2.82 (1H, td, 12.1 Hz, 3.3 Hz), 2.61-2.75 (3H, m), 2.35 (3H, s), 1.73 (1H, br. s); LCMS (6 minutes method): m/z 422 [M+H]+ @ Rt 3.36 min.

ii) (2R)-2-[(R)-{[2-(methylthio)phenyl]thio}(phenyl)methyl]morpholine hydrochloride

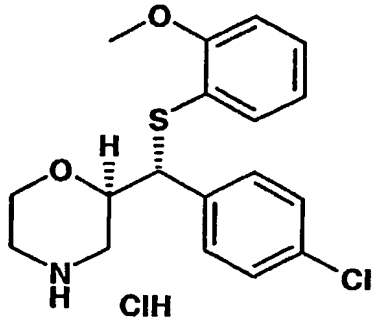


To a suspension of polymer supported Hunig's base (5.02 g) and (2R)-2-((R)-[phenyl]{[2-methylthiophenyl]thio}methyl)-4-benzylmorpholine and (2S)-2-((S)-[phenyl]{[2-methylthiophenyl]thio}methyl)-4-benzylmorpholine (4.02 g, 9.49 mmol) in

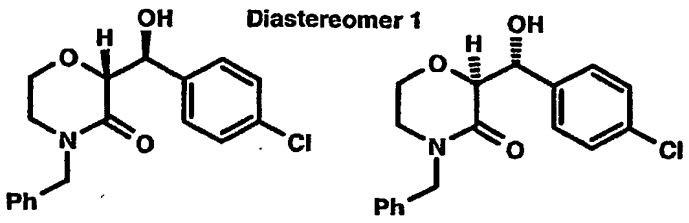
dry dichloromethane (70 ml) was added α-chloroethyl chloroformate (2.93 ml, 28.6 mmol, 3 eq.) at room temperature and under nitrogen. The mixture was heated at 40°C for 1.5 hours then left to stir at room temperature overnight. The reaction mixture was filtered and concentrated *in vacuo* to give a pale orange liquid. This was taken up in methanol (70 ml) and heated at 40°C for 2 hours. A white solid crashed out of the solution which was purified by SCX chromatography (eluent: ammonia/methanol 1/1 [v/v]). After evaporation *in vacuo* the product was obtained as a pale yellow oil (3.13 g, 99%); MW 331.50; $C_{18}H_{21}NOS_2$; ^{1}H NMR ($CDCl_3$): 7.03-7.15 (6H, m), 6.93-6.99 (2H, m), 6.74 (1H, td, 7.3 Hz, 1.5 Hz), 4.31 (1H, d, 7.8 Hz), 3.95 (1H, br. d, 12.1 Hz), 3.83 (1H, td, 8.1 Hz, 3.8 Hz), 3.59 (1H, td, 11.1 Hz, 2.8 Hz), 2.82 (1H, td, 12.1 Hz, 3.3 Hz), 2.61-2.75 (3H, m), 2.35 (3H, s), 1.73 (1H, br. s). After separation by chiral chromatography the oil was converted into its hydrochloride salt in which the pale yellow oil was taken up in isopropanol (~200 ml) and filtered. Addition of hydrogen chloride (19 ml of a 1M solution in diethyl ether, 19 mmol) gave a white precipitate to which further diethyl ether (~50 ml) was added. The solid was isolated by filtration, washed with diethyl ether give the hydrochloride salt of the title product as a white solid (3.03 g); MW 367.96; $C_{18}H_{22}ClNOS_2$; ^{1}H NMR ($CDCl_3$): 9.94 (2H, br. s), 7.06-7.18 (6H, m), 6.94-7.03 (2H, m), 6.78 (1H, t, 6.8 Hz), 4.24-4.32 (1H, m), 4.20 (1H, d, 5.8 Hz), 3.89-4.06 (2H, m), 3.18 (2H, br. t, 11.9 Hz), 2.99 (2H, br. s), 2.37 (3H, s); LCMS (10 minutes method): m/z 332 [M-Cl]+ @ Rt 5.07 min.

EXAMPLE 12

(2R)-2-((R)-[4-chlorophenyl]{[2-methoxyphenyl]thio}methyl)morpholine hydrochloride

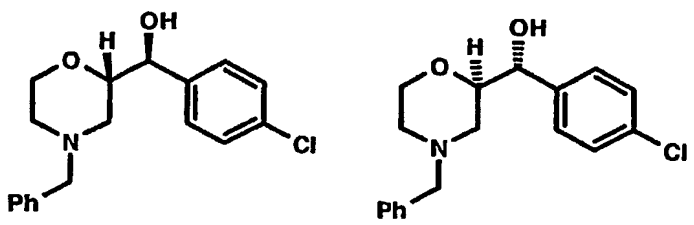


i)



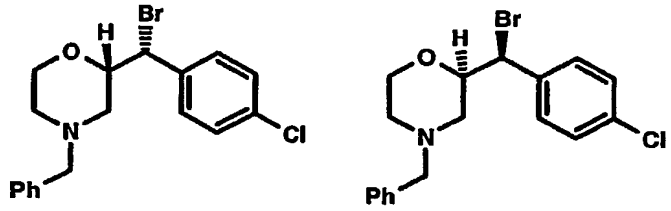
A solution of lithium diisopropylamide (2M in heptane, 18.2ml) was added dropwise over 20min to a stirred solution of 4-benzyl-morpholin-3-one (5.0g, 26mmol) and 4-chlorobenzaldehyde (4.41g, 31.4mmol) in dried tetrahydrofuran (60ml) cooled to –70°C under nitrogen atmosphere. After 1h at –70°C, the reaction mixture was quenched with aqueous ammonium chloride (100ml) and extracted with ethyl acetate (100ml). The extracts were washed with 2M aqueous hydrochloric acid (100ml), brine solution (100ml) and dried over sodium sulphate. After filtration, the solution was evaporated and the residual oil purified by chromatography on silica eluting with ethyl acetate:hexane 70:30 then ethyl acetate to give diastereomer 1 (2R)-2-[(S)-(4-chlorophenyl)(hydroxy)methyl]-4-benzylmorpholin-3-one and (2S)-2-[(R)-(4-chlorophenyl)(hydroxy)methyl]-4-benzylmorpholin-3-one as a solid (2.64g) followed by diastereomer 2 (2R)-2-[(R)-(4-chlorophenyl)(hydroxy)methyl]-4-benzylmorpholin-3-one and (2S)-2-[(S)-(4-chlorophenyl)(hydroxy)methyl]-4-benzylmorpholin-3-one as an oil (1.46g). Diastereomer 1 was recrystallised from ethyl acetate (25ml) n-hexane (100ml) to give white needles (2.47g, 29%)

ii)



A solution of borane in tetrahydrofuran (1M, 29ml) was added dropwise to a stirred solution of diastereomer 1 (2R)-2-[(S)-(4-chlorophenyl)(hydroxy)methyl]-4-benzylmorpholin-3-one and (2S)-2-[(R)-(4-chlorophenyl)(hydroxy)methyl]-4-benzylmorpholin-3-one (2.40g 7.24mmol) in dried tetrahydrofuran (30ml) at room temperature under nitrogen causing effervesence. The solution was heated to 60°C for 2h, allowed to cool to room temperature and excess borane quenched by adding methanol (14ml) slowly. Aqueous hydrochloric acid (1M, 14ml) was added, heated to 60°C for 1h and then evaporated to a white solid. Added saturated aqueous sodium carbonate (50ml) and diethyl ether (50ml) to dissolve the solid and extracted with diethyl ether (2x 50ml). The extracts were washed with brine solution, dried, filtered and evaporated to a colourless oil (2.38g). The oil was purified by chromatography on silica eluting with diethyl ether:hexane 75:25 to give (R)-[4-chlorophenyl][(2R)-4-benzylmorpholin-2-yl]methanol and (S)-[4-chlorophenyl][(2S)-4-benzylmorpholin-2-yl]methanol as a colourless oil (2.08g)

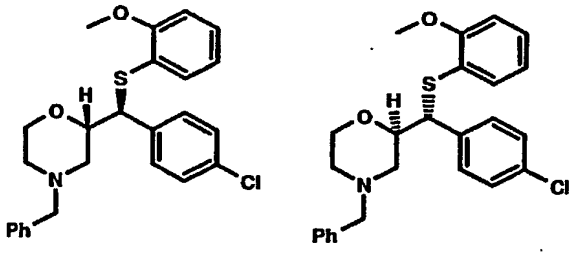
iii)



A solution of carbon tetrabromide (2.82g, 8.5mmol) in dichloromethane (3ml) was added dropwise over 10min to a stirred solution of (R)-[4-chlorophenyl][(2R)-4-benzylmorpholin-2-yl]methanol and (S)-[4-chlorophenyl][(2S)-4-benzylmorpholin-2-yl]methanol (1.80g, 5.67mmol) and triphenylphosphine (2.23g, 8.5mmol) in dichloromethane (40ml) at room temperature under nitrogen. After 30min, the reaction solution was washed with saturated aqueous sodium bicarbonate (50ml). The dichloromethane layer was dried, filtered and evaporated to a red liquid (8.5g). Trituration with diethyl ether (20ml) crystallised triphenylphoshine oxide that was then removed by filtration. The filtrate was evaporated to a yellow oil and was purified by chromatography

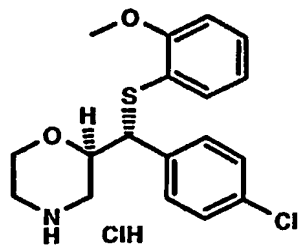
on silica eluting with ethyl acetate:hexane 20:80 to give a colourless oil of (2R)-2-[(S)-bromo(4-chlorophenyl)methyl]-4-benzylmorpholine and (2S)-2-[(R)-bromo(4-chlorophenyl)methyl]-4-benzylmorpholine (1.17g) that crystallised to a pink solid on standing.

iv)



Cesium carbonate (667mg, 2.05mmol) was added to a stirred solution of (2R)-2-[(S)-bromo(4-chlorophenyl)methyl]-4-benzylmorpholine and (2S)-2-[(R)-bromo(4-chlorophenyl)methyl]-4-benzylmorpholine (651mg, 1.71mmol) and 2-methoxybenzenethiol (287mg, 2.05mmol) in dry dimethylformamide (3ml). The suspension was heated to 90°C for 1h. The cooled reaction mixture was diluted with iced water, 2M aqueous sodium hydroxide (1ml) and extracted with diethyl ether (15ml). The extracts were washed with brine solution, dried, filtered and evaporated to a yellow oil (0.89g). The crude product was purified by chromatography on silica eluting with ethyl acetate:heptane 1:4 to give 2(R)-2-((R)-[4-chlorophenyl]{[2-methoxyphenyl]thio}methyl)-4-benzylmorpholine and 2(S)-2-((S)-[4-chlorophenyl]{[2-methoxyphenyl]thio}methyl)-4-benzylmorpholine as a pale yellow oil (619mg, 82%)

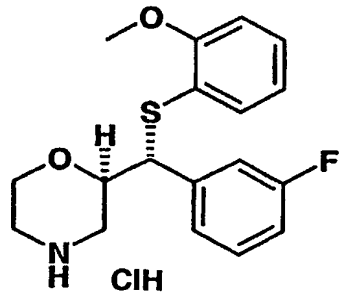
v)



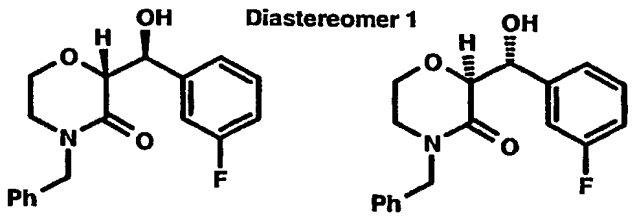
Alpha-chloroethyl chloroformate (0.3ml, 2.78mmol) was added to a gently stirred suspension of polystyrene supported diisopropylethylamine (Argonaut, 390mg, 1.39mmol) and 2(R)-2-((R)-[4-chlorophenyl]{[2-methoxyphenyl]thio}methyl)-4-benzylmorpholine and 2(S)-2-((S)-[4-chlorophenyl]{[2-methoxyphenyl]thio}methyl)-4-benzylmorpholine (610mg, 1.39mmol) in dichloromethane (8ml) at room temperature under nitrogen. After 3h, the suspension was filtered and the filtrate evaporated. The residue was dissolved in methanol (10ml) and heated to 60°C for 1h. The solution was evaporated and the solid residue crystallised from isopropanol (5ml) diethyl ether (10ml) to give a white solid (441mg, 82%). The racemic hydrochloride salt was converted to the free base by stirring in dicloromethane (20ml) and aqueous sodium hydroxide (1M, 20ml). The dichloromethane layer was separated, dried, filtered and evaporated to a colourless oil (403mg). Chiral preparative chromatography (Chiralcel-OD, heptane:ethanol:dimethylethylamine 50:50:0.2) was used to isolate the first eluting enantiomer Rt 9.3min as an oil. This was redissolved in diethylether and treated with ethereal hydrogen chloride to give the title product (2R)-2-((R)-[4-chlorophenyl]{[2-methoxyphenyl]thio}methyl)morpholine hydrochloride as a solid (159mg, 36%, mp 238-241°C), NMR (DMSO) 9.31 (2H, br. s), 7.32 (4H, dd), 7.07-7.20 (2H, m), 6.91 (1H,d), 6.76 (1H,t), 4.67 (1H, d), 4.0-4.1 (2H, br d), 3.78 (3H, s), 3.72 (1H, t), 3.15 (1H, d), 2.95-3.1 (3H, m) LCMS: *m/z* 350 $[M+H]^+$ @ Rt 3.8 min

EXAMPLE 13

(2R)-2-((R)-[3-fluorophenyl]{[2-methoxyphenyl]thio}methyl)morpholine hydrochloride

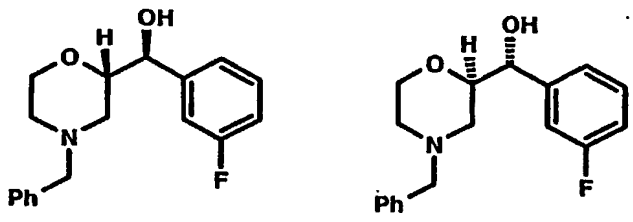


i)



A solution of lithium diisopropylamide (2M in heptane, 16.9ml) was added dropwise over 15min to a stirred solution of 4-benzyl-morpholin-3-one (5.0g, 26mmol) and 3-fluorobenzaldehyde (3.55g, 28.6mmol) in dried tetrahydrofuran (60ml) cooled to –70°C under nitrogen atmosphere. After 1h at –70°C, the reaction mixture was quenched with aqueous ammonium chloride (100ml) and extracted with ethyl acetate (100ml). The extracts were washed with 2M aqueous hydrochloric acid (2x 50ml), brine solution (100ml) and dried over sodium sulphate. After filtration, the solution was evaporated and the residual oil purified by chromatography on silica eluting with ethyl acetate:hexane 70:30 then ethyl acetate to give diastereomer 1 (2R)-2-[(S)-(3-fluorophenyl)(hydroxy)methyl]-4-benzylmorpholin-3-one and (2S)-2-[(R)-(3-fluorophenyl)(hydroxy)methyl]-4-benzylmorpholin-3-one as a solid (3.8g) followed by diastereomer 2 (2R)-2-[(R)-(3-fluorophenyl)(hydroxy)methyl]-4-benzylmorpholin-3-one and (2S)-2-[(S)-(3-fluorophenyl)(hydroxy)methyl]-4-benzylmorpholin-3-one as an oil (2.13g). Diastereomer 1 was recrystallised from ethyl acetate (25ml) n-hexane (100ml) to give white needles (2.62g, 32%)

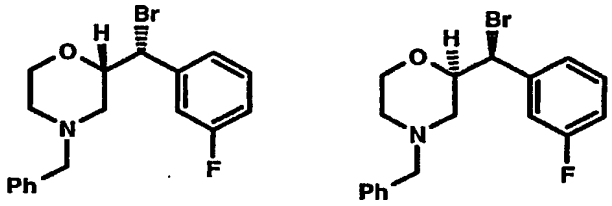
ii)



A solution of borane in tetrahydrofuran (1M, 30.7ml) was added dropwise to a stirred solution of diastereomer 1 (2R)-2-[(S)-(3-fluorophenyl)(hydroxy)methyl]-4-benzylmorpholin-3-one and (2S)-2-[(R)-(3-fluorophenyl)(hydroxy)methyl]-4-

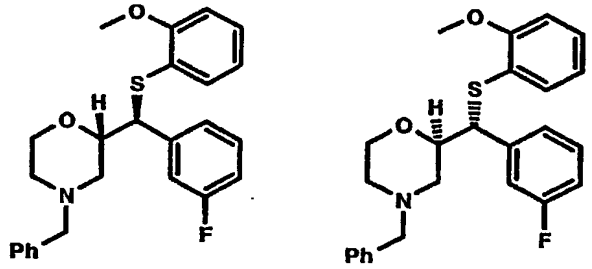
benzylmorpholin-3-one (2.42g 7.68mmol) in dried tetrahydrofuran (30ml) at room temperature under nitrogen causing effervesence. The solution was heated to 60°C for 2h, allowed to cool to room temperature and excess borane quenched by adding methanol (15ml) slowly. Aqueous hydrochloric acid (1M, 15ml) was added, heated to 60°C for 1h and then evaporated to a white solid. Added saturated aqueous sodium carbonate (50ml) and diethyl ether (50ml) to dissolve the solid and extracted with diethyl ether (2x 50ml). The extracts were washed with brine solution, dried, filtered and evaporated to a colourless oil (2.38g). The oil was purified by chromatography on silica eluting with diethyl ether:hexane 75:25 to give (R)-[3-fluorophenyl][(2R)-4-benzylmorpholin-2-yl]methanol and (S)-[3-fluorophenyl][(2S)-4-benzylmorpholin-2-yl]methanol as a colourless oil (2.23g)

iii)



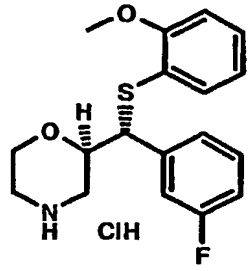
A solution of carbon tetrabromide (3.3g, 9.96mmol) in dichloromethane (4ml) was added dropwise over 5min to a stirred solution of (R)-[3-fluorophenyl][(2R)-4-benzylmorpholin-2-yl]methanol and (S)-[3-fluorophenyl][(2S)-4-benzylmorpholin-2-yl]methanol (2.0g, 6.64mmol) and triphenylphosphine (2.61g, 9.96mmol) in dichloromethane (40ml) at room temperature under nitrogen. After 30min, the reaction solution was washed with saturated aqueous sodium bicarbonate (50ml). The dichloromethane layer was dried, filtered and evaporated to a red liquid (8.5g). Trituration with diethyl ether (40ml) crystallised triphenylphoshine oxide that was then removed by filtration. The filtrate was evaporated to a yellow oil and was purified by chromatography on silica eluting with ethyl acetate:hexane 20:80 to give a colourless oil of (2R)-2-[(S)-bromo(3-fluorophenyl)methyl]-4-benzylmorpholine and (2S)-2-[(R)-bromo(3-fluorophenyl)methyl]-4-benzylmorpholine (0.811g, 34%).

iv)



Cesium carbonate (546mg, 1.68mmol) was added to a stirred solution of (2R)-2-[(S)-bromo(3-fluorophenyl)methyl]-4-benzylmorpholine and (2S)-2-[(R)-bromo(3-fluorophenyl)methyl]-4-benzylmorpholine (510mg, 1.4mmol) and 2-methoxybenzenethiol (235mg, 1.68mmol) in dry dimethylformamide (3ml). The suspension was stirred at room temperature for 4h. The reaction mixture was diluted with iced water, 2M aqueous sodium hydroxide (1ml) and extracted with diethyl ether (15ml). The extracts were washed with brine solution, dried, filtered and evaporated to a yellow oil (627mg). The crude product was purified by chromatography on silica eluting with ethyl acetate:heptane 20:80 to give 2(R)-2-((R)-[3-fluorophenyl]{[2-methoxyphenyl]thio}methyl)-4-benzylmorpholine and 2(S)-2-((S)-[3-fluorophenyl]{[2-methoxyphenyl]thio}methyl)-4-benzylmorpholine as a pale yellow oil (466mg, 79%)

v)

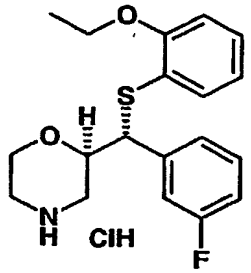


Alpha-chloroethyl chloroformate (0.235ml, 2.17mmol) was added to a gently stirred suspension of polystyrene supported diisopropylethylamine (Argonaut, 306mg, 1.09mmol) and 2(R)-2-((R)-[3-fluorophenyl]{[2-methoxyphenyl]thio}methyl)-4-benzylmorpholine and 2(S)-2-((S)-[3-fluorophenyl]{[2-methoxyphenyl]thio}methyl)-4-

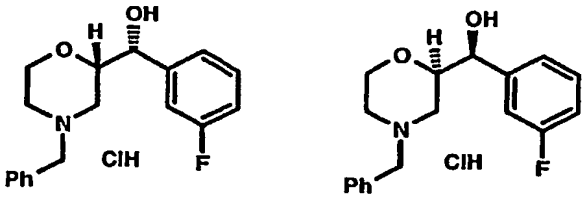
benzylmorpholine (460mg, 1.09mmol) in dichloromethane (6ml) at room temperature under nitrogen. After 16h, the suspension was filtered and the filtrate evaporated. The residue was dissolved in methanol (6ml) and heated to 60°C for 1h. The solution was evaporated and the solid residue crystallised from isopropanol (15ml) and n-hexane to give a white solid (371mg, 92%). The racemic hydrochloride salt was converted to the free base by stirring in dicloromethane (20ml) and aqueous sodium hydroxide (0.5M, 20ml). The dichloromethane layer was separated, dried, filtered and evaporated to a colourless oil (341mg). Chiral preparative chromatography (Chiralcel-OD, heptane:ethanol:dimethylethylamine 50:50:0.2) was used to isolate the first eluting enantiomer Rt 9.2min as an oil. This was redissolved in diethylether and treated with ethereal hydrogen chloride to give the title product (2R)-2-((R)-[3-fluorophenyl]{[2-methoxyphenyl]thio}methyl)morpholine hydrochloride as a solid (138mg, 34%, mp 233-234°C). NMR (DMSO) 9.26 (2H, br. s), 7.31 (1H, q), 7.10-7.20 (4H, m), 7.05 (1H, t), 6.92 (1H,d), 6.78 (1H, t), 4.66 (1H, d), 4.0-4.15 (2H, m), 3.77 (3H, s), 3.72 (1H, t), 3.19 (1H, d), 2.92-3.1 (3H, m). LCMS: *m/z* 334 $[M+H]^+$ @ Rt 3.5 min

EXAMPLE 14:

(2R)-2-((R)-[3-fluorophenyl]{[2-ethoxyphenyl]thio}methyl)morpholine hydrochloride

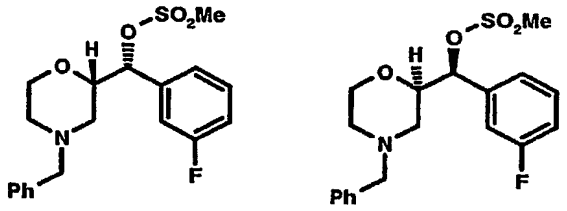


Method 1



A solution of borane in tetrahydrofuran (1M, 25.2ml) was added dropwise to a stirred solution of diastereomer 2 from example 13(i) (2R)-2-[(R)-(3-fluorophenyl)(hydroxy)methyl]-4-benzylmorpholin-3-one and (2S)-2-[(S)-(3-fluorophenyl)(hydroxy)methyl]-4-benzylmorpholin-3-one (2.0g 6.3mmol) in dried tetrahydrofuran (25ml) at room temperature under nitrogen causing effervesence. The solution was heated to 60°C for 1.5h, allowed to cool to room temperature and excess borane quenched by adding methanol (10ml) slowly. Aqueous hydrochloric acid (1M, 13ml) was added, heated to 60°C for 1h and then evaporated to a white solid. Added saturated aqueous sodium carbonate (50ml) and diethyl ether (50ml) to dissolve the solid and extracted with diethyl ether (2x 50ml). The extracts were washed with brine solution, dried, filtered and evaporated to a colourless oil (2.01g). The oil was dissolved in isopropanol (20ml) and ethereal hydrogen chloride (2M, 3ml) added to crystallise the salt (R)-[3-fluorophenyl][(2S)-4-benzylmorpholin-2-yl]methanol hydrochloride and (S)-[3-fluorophenyl][(2R)-4-benzylmorpholin-2-yl]methanol hydrochloride as a white solid (1.66g, 78%)

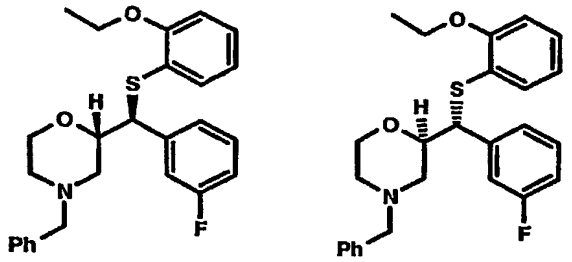
ii)



Methanesulphonyl chloride (1.01g, 8.9mmol) was added dropwise over 5min to a stirred solution of (R)-[3-fluorophenyl][(2S)-4-benzylmorpholin-2-yl]methanol hydrochloride and (S)-[3-fluorophenyl][(2R)-4-benzylmorpholin-2-yl]methanol hydrochloride (1.50g, 4.44mmol) and triethylamine (1.79g, 17.8mmol) in dry dichloromethane (30ml) at room temperature under nitrogen atmosphere. After 1h, water (30ml) was added, stirred vigorously and then the dichloromethane layer separated. The solution was dried over sodium sulphate, filtered and evaporated to a colourless oil. The oil was purified by chromatography on silica eluting with diethyl ether:hexane 3:1 to give (R)-[3-fluorophenyl][(2S)-4-benzylmorpholin-2-yl]methyl methanesulphonate and (S)-[3-

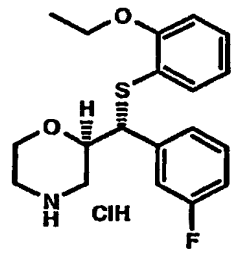
fluorophenyl][(2R)-4-benzylmorpholin-2-yl]methyl methanesulphonate as a colourless oil (1.51g, 90%)

iii)



Anhydrous potassium carbonate (276mg, 2mmol) was added to a stirred solution of (R)-[3-fluorophenyl][(2S)-4-benzylmorpholin-2-yl]methyl methanesulphonate and (S)-[3-fluorophenyl][(2R)-4-benzylmorpholin-2-yl]methyl methanesulphonate (682mg, 1.8mmol) and 2-ethoxybenzenethiol (308mg, 2mmol) in dry dimethylformamide (13ml) at room temperature under nitrogen atmosphere. After 3 days, water (25ml) was added and the mixture extracted with diethyl ether (25ml). The extracts were washed with brine solution (20ml), dried, filtered and evaporated to a yellow oil (0.89g). The product was purified by chromatography on silica eluting with ethyl acetate:heptane 20:80 to give 2(R)-2-((R)-[3-fluorophenyl]{[2-ethoxyphenyl]thio}methyl)-4-benzylmorpholine and 2(S)-2-((S)-[3-fluorophenyl]{[2-ethoxyphenyl]thio}methyl)-4-benzylmorpholine as a colourless oil (493mg, 63%).

iv)

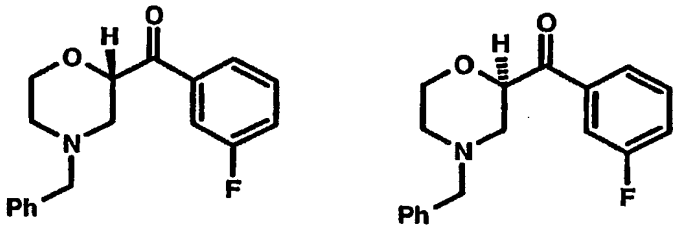


Debenzylation of 2(R)-2-((R)-[3-fluorophenyl]{[2-ethoxyphenyl]thio}methyl)-4-benzylmorpholine and 2(S)-2-((S)-[3-fluorophenyl]{[2-ethoxyphenyl]thio}methyl)-4-benzylmorpholine (480mg, 1.1mmol) using the method described in example 13(v) gave the racemic hydrochloride salt (360mg, 85%). After conversion to the free base, chiral

preparative chromatography (Chiralcel-OD, heptane:ethanol:dimethylethylamine 80:20:0.2) was used to isolate the first eluting enantiomer Rt 14.9min as an oil. This was redissolved in diethylether and treated with ethereal hydrogen chloride to give the title product (2R)-2-((R)-[3-fluorophenyl]{[2-ethoxyphenyl]thio}methyl)morpholine hydrochloride as a solid (144mg, 34%, mp 211-215°C). NMR (DMSO) 9.30 (2H, br. s), 7.31 (1H, q), 7.11-7.20 (4H, m), 7.05 (1H, t), 6.91 (1H,d), 6.79 (1H, t), 4.64 (1H, d), 3.97-4.15 (4H, m), 3.72 (1H, t), 3.19 (1H, d), 2.92-3.1 (3H, m), 1.37 (3H, t). LCMS: *m/z* 348 $[M+H]^+$ @ Rt 4.1 min

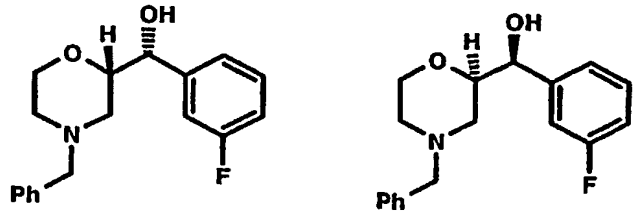
Method 2

i)



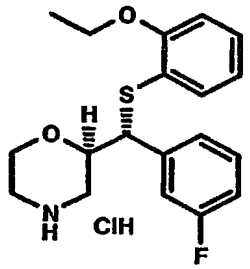
A solution of 3-fluorophenylmagnesium bromide (0.5M, 50ml, 25mmol) was added dropwise to a stirred solution of 4-benzyl-mopholin-2-carbonitrile (4.59g, 22.7mmol) in diethyl ether (50ml) at 0°C under nitrogen. After 45min at 0 C the mixture was allowed to warm to room temperature for 30min then recooled and quenched by the addition of aqueous hydrochloric acid (5M, 40ml) –caution exothermic. After 30min at room temperature, the acidic mixture was basified with sodium hydroxide (5M, 60ml) and extracted with ethyl acetate (3x 150ml). The combined extracts were washed with brine solution, dried, filtered and concentrated in vacuo to give (+/-)-(4-benzyl-morpholin-2-yl)-(3-fluorophenyl)methanone (6.9g) as a yellow oil.

ii)



Borontrifluoride etherate (27.6g, 194mmol) followed by trifluoroacetic acid (40ml) were added to a stirred solution of (+/-)-(4-benzyl-morpholin-2-yl)-(3-fluorophenyl)methanone (23.28g,77mmol) and triphenylsilane (81.1g, 311mmol) in dichloromethane (1000ml) at 0°C under nitrogen. After 16h at room temperature, reaction mixture was cooled and carefully basified by addition of aqueous sodium bicarbonate. The organic layer was separated, dried and concentrated in vacuo. The residual orange oil was purified using SCX-2 resin to absorb the amine product. Elution with methanolic ammonia (2M) and concentration in vacuo gave an oil (30g) that was further purified by chromatography on silica (toluene:diethyl ether 60:40) to give (R)-[3-fluorophenyl][(2S)-4-benzylmorpholin-2-yl]methanol and (S)-[3-fluorophenyl][(2R)-4-benzylmorpholin-2-yl]methanol as an oil (19.7g, 84%).

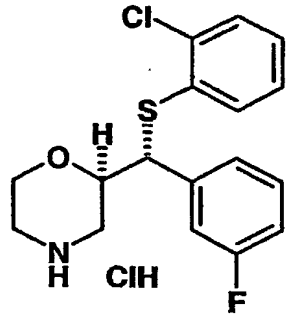
iii)



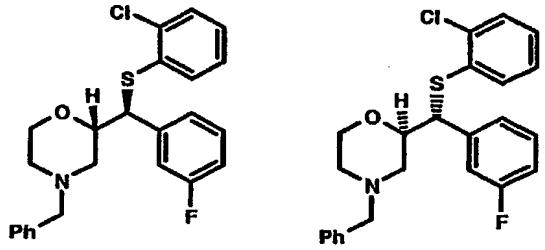
Convertion of (R)-[3-fluorophenyl][(2S)-4-benzylmorpholin-2-yl]methanol and (S)-[3-fluorophenyl][(2R)-4-benzylmorpholin-2-yl]methanol (19.7g) using method 1 in example 14(ii) gave (R)-[3-fluorophenyl][(2S)-4-benzylmorpholin-2-yl]methyl methanesulphonate and (S)-[3-fluorophenyl][(2R)-4-benzylmorpholin-2-yl]methyl methanesulphonate (24.7g) was followed by method 1 in example 14(iii) to give 2(R)-2-((R)-[3-fluorophenyl]{[2-ethoxyphenyl]thio}methyl)-4-benzylmorpholine and 2(S)-2-((S)-[3-fluorophenyl]{[2-ethoxyphenyl]thio}methyl)-4-benzylmorpholine (22.5g). This was debenzylated by method 1 in example 14(iv) to give (2R)-2-((R)-[3-fluorophenyl]{[2-ethoxyphenyl]thio}methyl)morpholine and (2S)-2-((S)-[3-fluorophenyl]{[2-ethoxyphenyl]thio}methyl)morpholine (15.2g) followed by preparative chiral chromatography to separate the first eluting enantiomer (7.7g) and then salt formation to the title product (2R)-2-((R)-[3-fluorophenyl]{[2-ethoxyphenyl]thio}methyl)morpholine hydrochloride (4.38g) as a white crystalline solid.

EXAMPLE 15

(2R)-2-((R)-[3-fluorophenyl]{[2-chlorophenyl]thio}methyl)morpholine hydrochloride

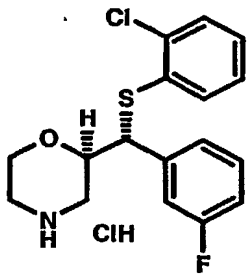


i)



Anhydrous potassium carbonate (377mg, 2.73mmol) was added to a stirred solution of (R)-[3-fluorophenyl][(2S)-4-benzylmorpholin-2-yl]methyl methanesulphonate and (S)-[3-fluorophenyl][(2R)-4-benzylmorpholin-2-yl]methyl methanesulphonate (740mg, 1.8mmol) and 2-chlorobenzenethiol (393mg, 2.73mmol) in dry dimethylformamide (10ml) at room temperature under nitrogen atmosphere. After 44h, diluted with methanol (15ml) and the inorganic solid filtered. The filtrate was poured directly onto SCX-2 columns (3x 10g), washed with methanol and the basic product eluted with methanolic ammonia (2M) to give a yellow oil (707mg) after evaporation. The product was further purified by chromatography on silica eluting with ethyl acetate:heptane 20:80 to give 2(R)-2-((R)-[3-fluorophenyl]{[2-chlorophenyl]thio}methyl)-4-benzylmorpholine and 2(S)-2-((S)-[3-fluorophenyl]{[2-chlorophenyl]thio}methyl)-4-benzylmorpholine as a colourless oil (653mg, 78%).

ii)

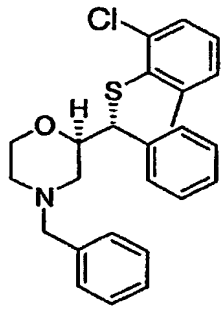


Alpha-chloroethyl chloroformate (0.33ml, 3.06mmol) was added to a gently stirred suspension of polystyrene supported diisopropylethylamine (Argonaut, 429mg, 1.53mmol) and 2(R)-2-((R)-[3-fluorophenyl]{[2-chlorophenyl]thio}methyl)-4-benzylmorpholine and 2(S)-2-((S)-[3-fluorophenyl]{[2-chlorophenyl]thio}methyl)-4-benzylmorpholine (429mg, 1.53mmol) in dichloromethane (10ml) at room temperature under nitrogen. After 2h, the suspension was filtered and the filtrate evaporated. The residue was dissolved in methanol (10ml) and heated to 60°C for 1h. The solution was evaporated to the hydrochloride salt, redissolved in methanol and converted to the free base using SCX-2 column (10g) eluting with methanol and then methanolic ammonia (2M) to give a colourless oil (501mg, 97%). Chiral preparative chromatography (Chiralcel-OJ, heptane:isopropanol:dimethylethylamine 90:10:0.2) was used to isolate the first eluting enantiomer Rt 19.2min as an oil. This was redissolved in diethylether and treated with ethereal hydrogen chloride to give the title product (2R)-2-((R)-[3-fluorophenyl]{[2-chlorophenyl]thio}methyl)morpholine hydrochloride as a solid (231mg, 40%, mp 183-7°C). NMR (DMSO) 9.38 (2H, br. s), 7.15-7.47 (7H, m), 7.09 (1H, t), 4.85 (1H, d), 4.12-4.20 (1H, m), 4.08 (1H, d), 3.77 (1H, t), 3.20 (1H, d), 2.95-3.10 (3H, m). LCMS: *m/z* 338/340 $[M+H]^+$ @ Rt 3.9 min

EXAMPLE 16

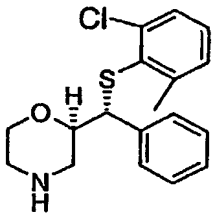
(2R)-2-[(R)-(2-chloro-6-methylphenyl)thio](phenyl)methyl]morpholine hydrochloride

i)



To a solution of (2R)-4-benzyl-2 [(S)-bromo(phenyl)methyl]morpholine (200 mg, 0.6 mmol) and 2-chloro-6-methyl thiophenol (0.167ml, 6eq) in anhydrous DMF (5 ml) at room temperature under nitrogen was added potassium carbonate (100 mg, 0.7mmol, 1.2eq). The reaction mixture was stirred at room temperature for 5 hours. The reaction mixture was diluted with methanol and poured directly onto a SCX-2 column for purification to give (2R)-2-[(R)-(2-chloro-6-methylphenyl)thio](phenyl)methyl]-4-(phenyl)methyl]morpholine before taking directly onto the next step.

ii) (2R)-2-[(R)-(2-chloro-6 methylphenyl)thio](phenyl)methyl]morpholine hydrochloride

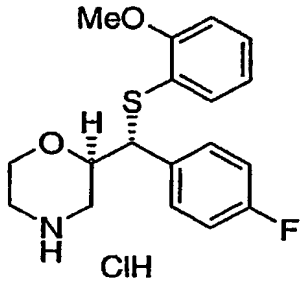


To a suspension of polymer supported Hunig's base (182mg, 3eq) and (2R)-2-[(R)-(2-chloro-6 methylphenyl)thio](phenyl)methyl]-4-(phenyl)methyl]morpholine (254mg, 0.6mmol) in dry DCM (5 ml) was added α-chloroethyl chloroformate (0.187ml, 1.7mmol, 3 eq) at room temperature and under nitrogen. The mixture was allowed to stir at room temperature overnight. The reaction mixture was taken up in methanol (5 ml) and stirred at room temperature overnight. The reaction mixture was then treated with SCX-2 (10 g). After elution with methanol followed by elution with 7 N NH_3/methanol (2R)-2-[(R)-(2-chloro-6 methylphenyl)thio](phenyl)methyl]morpholine was obtained as an oil (163 mg, 82% yield); MW 333; $C_{18}H_{20}ClNOS$; ^1H NMR (DMSO): 8.80 (1H, br s), 7.30

(1H, m), 7.20 (7H, m), 4.40 (1H, d, 8.2 Hz), 4.20 (1H, m), 4.00 (1H, m), 3.80 (1H, m), 3.15 (1H, m), 2.90 (2H, m), 2.20 (3H, s) 1.20 (1H, m); LCMS (10 minutes method): *m/z* 334[M+H]$^+$ @ R_T 5.1 min; HPLC purity = 100% (UV_{215nm}) / 100% (ELS). The free base was converted into the title product HCl salt.

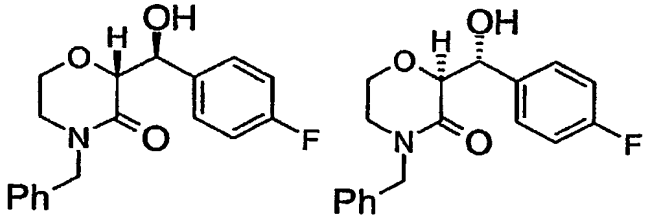
EXAMPLE 17:

(2R)-2-((R)-[4-fluorophenyl]{2-methoxyphenyl]thio}methyl)morpholine hydrochloride



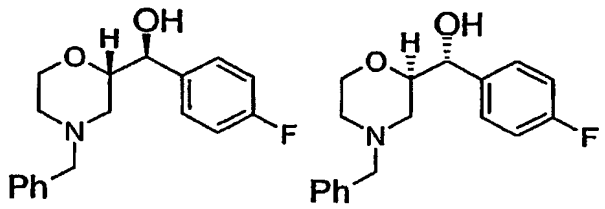
i)

Diastereomer 1



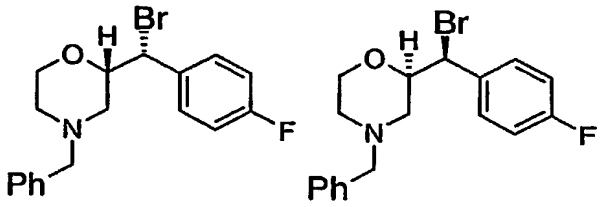
Following the procedure described in example 5(i), 4-benzylmorpholin-3-one (4.06g) was converted to 2-(R)-2-[(S)-(4-fluorophenyl)(hydroxy)methyl]-4-benzylmorpholin-3-one and 2-(S)-2-[(R)-(4-fluorophenyl)(hydroxy)methyl]-4-benzylmorpholin-3-one. Crystallised from hexane-ethyl acetate to give a colourless solid (2.04g).

ii)



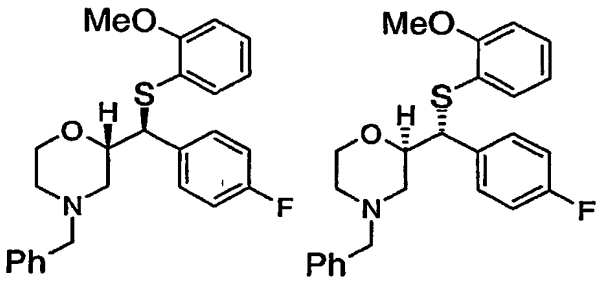
2-(R)-2-[(S)-(4-fluorophenyl)(hydroxy)methyl]-4-benzylmorpholin-3-one and 2-(S)-2-[(R)-(4-fluorophenyl)(hydroxy)methyl]-4-benzylmorpholin-3-one (2.0g) was converted to (R)-[4-fluorophenyl][(2R)-4-benzylmorpholin-2-yl]methanol and (S)-[4-fluorophenyl][(2S)-4-benzylmorpholin-2-yl]methanol following procedure described in example 2(ii) to give a colourless oil (1.88g).

iii)



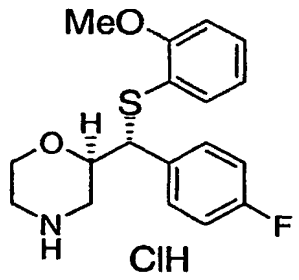
To a stirred solution of (R)-[4-fluorophenyl][(2R)-4-benzylmorpholin-2-yl]methanol and (S)-[4-fluorophenyl][(2S)-4-benzylmorpholin-2-yl]methanol (1.64g, 5.54mmol)) and triphenylphosphine (2.32g, 8.86mmol) in anhydrous chloroform (40ml) was added solid carbon tetrabromide (2.76g, 8.31mmol) in one lot. The solution was heated at reflux under nitrogen for 3h. Cooled and washed reaction mixture with brine, dried, filtered and evaporated to a red oil. The oil was purified by chromatography on silica eluting with hexane:ethyl acetate 41:9 to give 2(R)-2-[(S)-bromo(4-fluorophenyl)methyl]-4-benzylmorpholine and 2(S)-2-[(R)-bromo(4-fluorophenyl)methyl]-4-benzylmorpholine as a colourless oil (0.49g)

iv)



To a stirred suspension of 2(R)-2-[(S)-bromo(4-fluorophenyl)methyl]-4-benzylmorpholine and 2(S)-2-[(R)-bromo(4-fluorophenyl)methyl]-4-benzylmorpholine (0.6g, 1.65mmol) and cesium carbonate (0.59g, 1.81mmol) in dry DMF (5ml) was added 2-methoxybenzenethiol (0.25g, 1.81mmol). The suspension was heated at 90°C under nitrogen for 3h. The cooled reaction mixture was diluted with water and extracted with diethyl ether. The extracts were washed with water and brine, dried, filtered and evaporated to an oil. The crude oil was purified by chromatography on silica eluting with hexane:ethyl acetate 4:1 then 3:2 to give (2*R*)-2-((*R*)-(4-fluorophenyl){[2-methoxyphenyl]thio}methyl)morpholine and (2*S*)-2-((*S*)-(4-fluorophenyl){[2-methoxyphenyl]thio}methyl)morpholine a colourless oil (0.22g)

v)



Reaction of the mixture of (2*R*)-2-((*R*)-(4-fluorophenyl){[2-methoxyphenyl]thio}methyl)morpholine and (2*S*)-2-((*S*)-(4-fluorophenyl){[2-methoxyphenyl]thio}methyl)morpholine (430 mg, 1.02 mmol) following procedure described in EXAMPLE 1(iv) gave a colourless oil (340 mg, 90% yield) from which first eluting enantiomer (2*R*)-2-((*R*)-(4-fluorophenyl){[2-methoxyphenyl]thio}methyl)morpholine was obtained after chiral chromatography on a Chiralcel-OD column eluant heptane/isopropanol/dimethylethylamine (50/50/0.2): Rt

10.58 min. This was converted into its hydrochloride salt. ^{1}H NMR (CD_3OD): 7.01-7.20 (4H, m), 6.70-6.80 (3H, m), 6.60 (1H, t), 4.37 (1H, d,), 3.82-3.90 (1H, m), 3.70-3.79 (4H, m), 3.49-3.60 (1H, m), 2.70-2.78 (2H, m),.2.60-2.70 (2H, m).

The compounds of the present invention may be used as medicaments in human or veterinary medicine. The compounds may be administered by various routes, for example, by oral or rectal routes, topically or parenterally, for example by injection, and are usually employed in the form of a pharmaceutical composition.

Such compositions may be prepared by methods well known in the pharmaceutical art and normally comprise at least one active compound in association with a pharmaceutically acceptable diluent or carrier. In making the compositions of the present invention, the active ingredient will usually be mixed with a carrier or diluted by a carrier, and/or enclosed within a carrier which may, for example, be in the form of a capsule, sachet, paper or other container. Where the carrier serves as a diluent, it may be solid, semi-solid, or liquid material which acts as a vehicle, excipient or medium for the active ingredient. Thus, the composition may be in the form of tablets, lozenges, sachets, cachets, elixirs, suspensions, solutions, syrups, aerosol (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, injection solutions and suspensions and sterile packaged powders.

Some examples of suitable carriers are lactose, dextrose, vegetable oils, benzyl alcohols, alkylene glycols, polyethylene glycols, glycerol triacetate, gelatin, carbohydrates such as starch and petroleum jelly, sucrose sorbitol, mannitol, starches, gum acacia,calcium phosphate, alginates, tragacanth, gelatin, syrup, methyl cellulose, methyl- and propyl- hydrobenzoate, talc, magnesium stearate and mineral oil. The compounds of formula (I) can also be lyophilized and the lyophilizates obtained used, for example, for the production of injection preparations. The preparations indicated can be sterilized and/or can contain auxiliaries such as lubricants, preservatives, stabilizers and/or wetting agents, emulsifiers, salts for affecting the osmotic pressure, buffer substances, colourants, flavourings and/or one or more further active compounds, e.g. one or more vitamins. Compositions of the invention may be formulated so as to provide,

quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

The compositions are preferably formulated in a unit dosage form, each dosage containing from about 5 to about 500 mg, more usually about 25 to about 300 mg, of the active ingredient. The term "unit dosage form" refers to physically discrete units suitable as unitary doses for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical carrier.

The pharmacological profile of the present compounds may be demonstrated as follows.

Scintillation proximity assays for determining the affinity of test ligands at the norepinephrine and serotonin transporters.

The compounds of the invention are norepinephrine and serotonin reuptake inhibitors, and possess excellent activity in, for example, a scintillation proximity assay (e.g. J. Gobel, D.L. Saussy and A. Goetz, J. Pharmacol. Toxicolo. (1999), 42, 237-244). Thus ^{3}H-nisoxetine binding to norepinephrine re-uptake sites in a cell line transfected with human norepinephrine transporter binding protein and similarly ^{3}H-citalopram binding to serotonin re-uptake sites in a cell line transfected with human serotonin transporter binding protein have been used to determine the affinity of ligands at the norepinephrine and serotonin transporters respectively.

Formalin Paw Assay

The analgesic effect of compounds of the invention for the treatment of persistent nociceptive pain was demonstrated using the well-known "formalin test." The formalin test is a model of persistent nociceptive activation induced by tissue injury which can lead to central sensitization. (Shibata, M., Ohkubo, T., Takahashi, H., and Inoki, R., "Modified formalin test: Characteristic biphasic pain response," *Pain* (1989) 38: 347-352; and Tjolsen, A., Berge, O.G., Hunskaar, S., Rosland, J.H., and Hole, K., "The formalin test: an evaluation of the method," *Pain* (1992) 51:5-17.) The effect of compounds of the invention on formalin-induced paw-licking behavior in the rat was investigated as an index of persistent nociceptive activation. In this test, the injection of formalin under the

skin on the dorsal lateral surface of the hind paw of rats causes an immediate and intense increase in the spontaneous activity of C fiber afferents. This activation evokes a distinctly quantifiable behavior indicative of pain, such as licking of the injected paw. The behavioral response to formalin is biphasic, with an early phase that is short lived, followed by an extended tonic response or late phase of persistent nociceptive activation. Mechanisms causing the late phase response, such as central sensitization of pain transmitting neurons, are currently believed to contribute to various types of persistent pains.

Male Sprague-Dawley rats (200-250g; Charles River, Portage, MI) were maintained at constant temperature and light (12h light/12h dark) for 4-7 days prior to the studies. Animals had free access to food and water at all times prior to the day of the experiment.

The formalin test was performed in custom made Plexiglas® boxes 25x25x20 cm (length x width x height) in size. A mirror placed at the back of the box allowed the unhindered observation of the formalin injected paw. Rats were acclimatized individually in the cubicles at least 1 hour prior to the experiment. All testing was conducted between 08:00 and 14:00 hr and the testing room temperature was maintained at 21-23 ^{o}C. Test compound was administered 30 or 60 minutes prior to the formalin injection. Formalin (50 μl of a 5% solution in saline) was injected subcutaneously into the dorsal lateral surface of the right hind paw with a 27 gauge needle. Observation started immediately after the formalin injection. Formalin-induced pain was quantified by recording in 5 minute intervals the number of formalin injected paw licking events and the number of seconds each licking event lasted. These recordings were made for 50 minutes after the formalin injection. Scoring in the formalin test was performed according to Coderre *et al.*, 1993b and Abbott *et al.*, 1995. (Coderre T.J., Fundytus M.E., McKenna J.E., Dalal S. and Melzack R. "The formalin test: a validation of the weighted-scores method of the behavioral pain rating," *Pain*(1993b) **54:** 43-50; and Abbott F.V., Franklin K.B.J. and Westbrook R.F. "The formalin test: scoring properties of the first and second phases of the pain response in rats," *Pain* (1995) **60:** 91-102.) The sum of time spent licking in seconds from time 0 to 5 minutes was considered the early phase while the late phase was taken as the sum of seconds spent licking from 15 to 40 minutes.

In Vitro Determination of the Interaction of compounds with CYP2D6 in Human Hepatic Microsomes

Principle

The interaction of compounds with CYP2D6 was evaluated by the measurement of the inhibition of the bufurolol 1'-hydroxylase activity by the compounds.

Assay description

Bufuralol 1-hydroxylase activity is determined by using 0.5 mg/ml human liver microsomal protein (human biologics), 10 μmol/L bufuralol, in 0.1 M sodium phosphate buffer pH 7.4, incubated for 5 min at 37°C in the presence of 2 mM βNADPH, with 0, 5 or 25 μM of the test compound (inhibitor). The compound was dissolved in acetonitrile, such that the final concentration of acetonitrile in the incubation was 0.5%. The total reaction volume was 100 μl. The reaction was terminated by addition of 75 μl of methanol followed by centrifugation. 40 μl of the supernatant was analysed by HPLC.

Analysis conditions

A Beckman Ultrasphere C_{18} column (5 μm, 250 x 4.6 mm) was used, with a 13 minute gradient from 100% of solvent A (0.02 M potassium dihydrogen phosphate buffer pH 3/methanol (65/35)) to 100 % of solvent B (0.02 M potassium dihydrogen phosphate buffer pH 3/methanol (20/80)), according to the following gradient. The run time was 20 minutes. Formation of 1'-hydroxybufuralol was detected by fluorimetric detection with extinction at λ 252 nm and emission at λ 302 nm.

Time (min)	Solvent A (%)	Solvent B (%)
0	100	0
8	0	100
12	0	100
13	100	0

Calculation of the results

The percent of inhibition is calculated as follows:

$$100 - \frac{100 \times \text{1'-hydroxybufuralol area formed with inhibitor}}{\text{1'-hydroxybufuralol area formed without inhibitor}}$$

The IC_{50} is calculated from the percent inhibition as follows (assuming competitive inhibition): $\frac{\text{Compound Concentration} \times (100 - \text{Percent of inhibition})}{\text{Percent of inhibition}}$

The IC_{50} estimation is assumed valid if inhibition is between 20% and 80% (Moody 1999).

X-RAY CRYSTALLOGRAPHIC DATA

Table 1. Crystal data and structure refinement for 2003xf.

	Identification code	2003xf	
	Empirical formula	C18 H19 Cl F3 N O S	
	Formula weight	389.85	
	Temperature	107(2) K	
	Wavelength	0.71073 A	
	Crystal system, space group	Monoclinic, P2(1)	
	Unit cell dimensions	a = 9.984(2) A	alpha = 90 deg.
		b = 5.6484(13) A	beta = 100.867(4) deg.
		c = 15.931(4) A	gamma = 90 deg.
	Volume	882.4(4) A^3	
	Z, Calculated density	2, 1.467 Mg/m^3	
	Absorption coefficient	0.371 mm^-1	
	F(000)	404	
	Crystal size	.06 x .08 x .18 mm	
	Theta range for data collection	1.30 to 28.20 deg.	
	Limiting indices	11<=h<=13, -7<=k<=7, -20<=l<=19	
	Reflections collected / unique	5986 / 3378 [R(int) = 0.0661]	
	Completeness to theta = 28.20	92.9 %	
	Absorption correction	None	
	Refinement method	Full-matrix least-squares on F^2	
	Data / restraints / parameters	3378 / 1 / 234	
	Goodness-of-fit on F^2	0.846	
	Final R indices [I>2sigma(I)]	R1 = 0.0488, wR2 = 0.0908	
	R indices (all data)	R1 = 0.1227, wR2 = 0.1101	
	Absolute structure parameter	0.11(10)	
	Largest diff. peak and hole	0.548 and -0.444 e.A^-3	

X-RAY CRYSTALLOGRAPHIC DATA

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for 2003xf.

U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)	
	S(8)	8641(1)	5291(2)	2641(1)	35(1)
	O(1)	10279(3)	2645(5)	4200(2)	24(1)
	C(7)	9992(5)	3088(8)	2678(3)	25(1)
	F(3)	5136(4)	4842(7)	443(2)	65(1)
	N(4)	13055(4)	1352(9)	4386(3)	21(1)
	C(5)	12147(4)	1431(8)	3536(3)	22(1)
	F(2)	7264(4)	4253(5)	644(2)	51(1)
	C(20)	10490(5)	1794(8)	1263(3)	31(1)
	F(1)	6497(4)	7227(5)	1228(2)	48(1)
	C(15)	10669(5)	3416(8)	1925(3)	24(1)
	C(6)	11008(5)	3187(8)	3525(3)	24(1)
	C(16)	11472(5)	5394(10)	1846(3)	32(1)
	C(10)	6184(5)	3389(9)	1805(3)	26(1)
	C(13)	5978(5)	382(11)	3117(4)	40(1)
	C(9)	7190(5)	3438(9)	2506(3)	30(1)
	C(3)	12283(5)	976(8)	5085(3)	27(1)
	C(12)	4992(5)	364(10)	2423(3)	31(1)
	C(2)	11168(5)	2787(9)	5010(3)	28(1)
	C(21)	6253(6)	4934(11)	1033(4)	41(2)
	C(18)	11846(5)	4080(10)	494(3)	33(1)
	C(17)	12048(5)	5721(9)	1131(4)	36(1)
	C(19)	11078(5)	2138(9)	552(4)	35(1)
	C(11)	5062(5)	1943(9)	1738(4)	42(2)
	C(14)	7065(6)	1852(10)	3160(4)	43(2)
	Cl(1)	4131(1)	6360(2)	4214(1)	30(1)

X-RAY CRYSTALLOGRAPHIC DATA

Table 3. Bond lengths [A] and angles [deg] for 2003xf.

	S(8)-C(9)	1.767(5)
	S(8)-C(7)	1.828(5)
	O(1)-C(2)	1.424(5)
	O(1)-C(6)	1.440(5)
	C(7)-C(15)	1.495(6)
	C(7)-C(6)	1.528(6)
	F(3)-C(21)	1.318(6)
	N(4)-C(5)	1.481(5)
	N(4)-C(3)	1.484(6)
	C(5)-C(6)	1.507(6)
	F(2)-C(21)	1.337(6)
	C(20)-C(19)	1.385(7)
	C(20)-C(15)	1.383(6)
	F(1)-C(21)	1.343(6)
	C(15)-C(16)	1.395(6)
	C(16)-C(17)	1.382(7)
	C(10)-C(9)	1.354(6)
	C(10)-C(11)	1.374(7)
	C(10)-C(21)	1.520(8)
	C(13)-C(12)	1.334(6)
	C(13)-C(14)	1.358(7)
	C(9)-C(14)	1.397(7)
	C(3)-C(2)	1.500(6)
	C(12)-C(11)	1.421(7)
	C(18)-C(19)	1.351(7)
	C(18)-C(17)	1.360(7)
	C(9)-S(8)-C(7)	100.6(2)
	C(2)-O(1)-C(6)	110.4(4)
	C(15)-C(7)-C(6)	112.3(4)
	C(15)-C(7)-S(8)	109.4(3)
	C(6)-C(7)-S(8)	111.5(3)
	C(5)-N(4)-C(3)	112.0(4)
	N(4)-C(5)-C(6)	11.2(4)
	C(19)-C(20)-C(15)	121.2(5)

	C(20)-C(15)-C(16)	117.1(5)
	C(20)-C(15)-C(7)	121.1(5)
	C(16)-C(15)-C(7)	121.8(5)
	O(1)-C(6)-C(5)	109.7(4)
5	O(1)-C(6)-C(7)	107.9(4)
	C(5)-C(6)-C(7)	111.1(4)
	C(17)-C(16)-C(15)	121.2(5)
	C(9)-C(10)-C(11)	122.9(5)
	C(9)-C(10)-C(21)	121.0(5)
10	C(11)-C(10)-C(21)	116.0(5)
	C(12)-C(13)-C(14)	120.3(6)
	C(10)-C(9)-C(14)	116.4(5)
	C(10)-C(9)-S(8)	125.2(4)
	C(14)-C(9)-S(8)	118.4(4)
15	N(4)-C(3)-C(2)	109.0(4)
	C(13)-C(12)-C(11)	119.7(5)
	O(1)-C(2)-C(3)	111.1(4)
	F(3)-C(21)-F(1)	107.1(5)
	F(3)-C(21)-F(2)	105.6(5)
20	F(1)-C(21)-F(2)	105.4(5)
	F(3)-C(21)-C(10)	113.2(5)
	F(1)-C(21)-C(10)	113.6(5)
	F(2)-C(21)-C(10)	111.4(5)
	C(19)-C(18)-C(17)	120.6(5)
25	C(18)-C(17)-C(16)	119.8(5)
	C(18)-C(19)-C(20)	120.2(5)
	C(10)-C(11)-C(12)	118.1(5)
	C(13)-C(14)-C(9)	122.5(5)

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30 Symmetry transformations used to generate equivalent atoms:

X-RAY CRYSTALLOGRAPHIC DATA

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for 2003xf.

The anisotropic displacement factor exponent takes the form: -2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
S(8)	24(1)	24(1)	53(1)	-1(1)	-1(1)	4(1)
O(1)	24(2)	23(2)	24(2)	3(2)	0(2)	-2(2)
C(7)	20(3)	23(2)	27(3)	-3(2)	-8(3)	0(2)
F(3)	55(2)	88(3)	42(2)	15(2)	-16(2)	-13(2)
N(4)	19(2)	14(2)	31(3)	3(2)	3(2)	-3(3)
C(5)	22(3)	16(2)	26(3)	-4(2)	2(2)	2(3)
F(2)	69(3)	53(2)	39(2)	5(2)	29(2)	3(2)
C(20)	29(3)	28(3)	31(3)	-12(3)	-5(3)	-1(2)
F(1)	61(2)	35(2)	46(2)	5(2)	5(2)	5(2)
C(15)	20(3)	22(3)	27(3)	2(3)	-3(2)	5(2)
C(6)	23(3)	17(2)	33(3)	-1(2)	11(3)	1(2)
C(16)	40(3)	22(2)	31(3)	-3(3)	1(3)	-7(3)
C(10)	20(3)	30(3)	27(3)	2(3)	8(3)	4(3)
C(13)	33(3)	45(3)	42(4)	3(3)	7(3)	0(3)
C(9)	20(3)	38(3)	31(4)	-8(3)	2(3)	7(3)
C(3)	22(3)	28(3)	32(3)	10(2)	5(2)	0(2)
C(12)	22(3)	29(2)	41(4)	-1(3)	8(3)	-7(3)
C(2)	28(3)	34(3)	22(3)	-2(3)	3(3)	4(2)
C(21)	27(4)	50(4)	43(4)	-16(3)	-1(3)	10(3)
C(18)	24(3)	44(3)	30(4)	-1(3)	3(3)	11(3)
C(17)	42(4)	26(3)	40(4)	0(3)	9(3)	-6(2)
C(19)	33(3)	38(3)	33(4)	-9(3)	2(3)	6(3)
C(11)	20(3)	49(4)	52(4)	-18(3)	-3(3)	8(3)
C(14)	35(4)	72(5)	22(3)	16(3)	-1(3)	-4(3)
Cl(1)	24(1)	16(1)	46(1)	1(1)	-1(1)	-1(1)

X-RAY CRYSTALLOGRAPHIC DATA

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for 2003xf.

	x	y	z	U(eq)
H(7A)	9558	1486	2630	30
H(5A)	11757	-162	3392	26
H(5B)	12685	1877	3099	26
H(20A)	9954	420	1297	37
H(6A)	11398	4819	3611	29
H(16A)	11626	6536	2292	38
H(13A)	5919	-637	3583	48
H(3A)	12902	1128	5645	33
H(3B)	11886	-636	5043	33
H(12A)	4246	-700	2387	37
H(2A)	10639	2529	5468	34
H(2B)	11575	4389	5085	34
H(18A)	12248	4302	5	40
H(17A)	12584	7087	1084	43
H(19A)	10941	1005	103	42
H(11A)	4354	1998	1248	50
H(14A)	7767	1799	3653	52
H(4B)	13680(60)	2600(100)	4430(30)	53(19)
H(4A)	13580(50)	230(90)	4400(30)	29(17)

X-RAY CRYSTALLOGRAPHIC DATA

Table 6. Torsion angles [deg] for 2003xf.

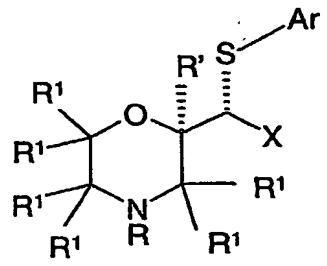
	C(9)-S(8)-C(7)-C(15)	115.5(4)
	C(9)-S(8)-C(7)-C(6)	-119.7(4)
	C(3)-N(4)-C(5)-C(6)	52.2(6)
	C(19)-C(20)-C(15)-C(16)	-0.4(7)
	C(19)-C(20)-C(15)-C(7)	177.8(4)
	C(6)-C(7)-C(15)-C(20)	126.4(5)
	S(8)-C(7)-C(15)-C(20)	-109.2(4)
	C(6)-C(7)-C(15)-C(16)	-55.5(6)
	S(8)-C(7)-C(15)-C(16)	68.9(5)
	C(2)-O(1)-C(6)-C(5)	60.7(5)
	C(2)-O(1)-C(6)-C(7)	-178.1(4)
	N(4)-C(5)-C(6)-O(1)	-55.1(5)
	N(4)-C(5)-C(6)-C(7)	-174.3(4)
	C(15)-C(7)-C(6)-O(1)	-175.0(4)
	S(8)-C(7)-C(6)-O(1)	61.9(4)
	C(15)-C(7)-C(6)-C(5)	-54.7(5)
	S(8)-C(7)-C(6)-C(5)	-177.8(3)
	C(20)-C(15)-C(16)-C(17)	0.7(7)
	C(7)-C(15)-C(16)-C(17)	-177.4(5)
	C(11)-C(10)-C(9)-C(14)	2.6(8)
	C(21)-C(10)-C(9)-C(14)	-176.4(5)
	C(11)-C(10)-C(9)-S(8)	-178.8(4)
	C(21)-C(10)-C(9)-S(8)	2.2(7)
	C(7)-S(8)-C(9)-C(10)	-114.6(5)
	C(7)-S(8)-C(9)-C(14)	64.0(5)
	C(5)-N(4)-C(3)-C(2)	-52.6(6)
	C(14)-C(13)-C(12)-C(11)	-1.9(8)
	C(6)-O(1)-C(2)-C(3)	-63.3(5)
	N(4)-C(3)-C(2)-O(1)	58.2(5)
	C(9)-C(10)-C(21)-F(3)	-173.8(5)
	C(11)-C(10)-C(21)-F(3)	7.1(7)
	C(9)-C(10)-C(21)-F(1)	-51.3(7)
	C(11)-C(10)-C(21)-F(1)	129.6(5)
	C(9)-C(10)-C(21)-F(2)	67.4(7)

	C(11)-C(10)-C(21)-F(2)	-111.6(5)
	C(19)-C(18)-C(17)-C(16)	0.5(8)
	C(15)-C(16)-C(17)-C(18)	-0.7(8)
	C(17)-C(18)-C(19)-C(20)	-0.2(8)
5	C(15)-C(20)-C(19)-C(18)	0.1(8)
	C(9)-C(10)-C(11)-C(12)	-2.7(8)
	C(21)-C(10)-C(11)-C(12)	176.3(5)
	C(13)-C(12)-C(11)-C(10)	2.3(8)
	C(12)-C(13)-C(14)-C(9)	1.9(8)
10	C(10)-C(9)-C(14)-C(13)	-2.1(8)
	S(8)-C(9)-C(14)-C(13)	179.2(4)

Symmetry transformations used to generate equivalent atoms

CLAIMS

1. A compound of formula (I)



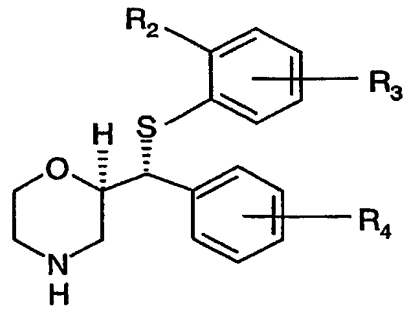
(I)

wherein

R is H;

Ar is an aromatic group selected from phenyl; X is a phenyl group; R' is H or C_1-C_4 alkyl; each R_1 is independently H or C_1-C_4 alkyl; and pharmaceutically acceptable salts thereof.

2. A compound as claimed in claim 1, represented by formula II:



(II)

in which R_2 and R_3 are each independently selected from H, C_1-C_4 alkyl, O(C_1-C_4 alkyl), S(C_1-C_4 alkyl), halo, and phenyl; and

R_4 is selected from H, C_1-C_4 alkyl, O(C_1-C_4 alkyl) and halo; and pharmaceutically acceptable salts thereof.

3. A compound as claimed in any one of claims 1 and 2, wherein R_2 is selected from C_1-C_2 alkyl, O(C_1-C_2 alkyl), S(C_1-C_2 alkyl), Cl and F.

4. A compound as claimed in any one of the preceding claims, wherein R_3 is selected from H, Me and Cl.

5. A compound as claimed in any one of the preceding claims, wherein R_4 is selected from H, C_1-C_2 alkyl, O(C_1-C_2 alkyl), Cl and F.

6. A compound as claimed in any one of claims 1-5, for use as a pharmaceutical.

7. A compound as claimed in any one of claims 1-5, for use as a selective inhibitor of the reuptake of serotonin and norepinephrine.

8. The use of a compound as claimed in any one of claims 1-5, for treating a disorder associated with serotonin and norepinephrine dysfunction in mammals.

9. The use of a compound as claimed in any one of claims 1-5, for the manufacture of a medicament for treating a disorder associated with serotonin and norepinephrine dysfunction in mammals.

10. A method for selectively inhibiting the reuptake of serotonin and norepinephrine in mammals, comprising administering to a patient in need thereof an effective amount of a compound as claimed in any one of claims 1-5.

11. A method for treating a disorder associated with serotonin and norepinephrine dysfunction in mammals, comprising administering to a patient in need thereof an effective amount of a compound as claimed in any one of claims 1-5.

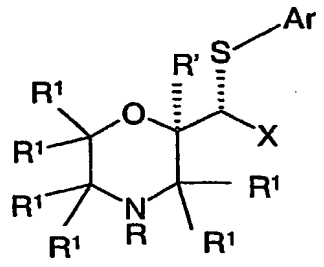
12. A method or use as claimed in any one of claims 8, 9 and 11, wherein the disorder is selected from depression, OCD, anxiety, memory loss, urinary incontinence, conduct disorders, ADHD, obesity, alcoholism, smoking cessation and pain.

13. A method or use as claimed in any one of claims 8, 9 and 11, wherein the disorder is selected from depression, stress urinary incontinence and pain.

14. A method or use as claimed in any one of claims 8, 9 and 11, wherein the disorder is pain.

ABSTRACT

A compound of formula (I)



(I)

wherein

R is H;

Ar is an aromatic group selected from phenyl; X is a phenyl group; R' is H or C_1-C_4 alkyl; each R_1 is independently H or C_1-C_4 alkyl; and pharmaceutically acceptable salts thereof.

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